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ABSTRACT

The present invention provides fully human antibodies that bind to either toxin A or toxin B of *Clostridium difficile,* or to both toxin A and toxin B, compositions comprising the antibodies and methods of use. The antibodies of the invention are useful for neutralizing the toxins from *C. difficile,* thus providing a means of treating the disease and symptoms associated with a *C. difficile* infection, including the treatment of diarrhea, or pseudomembranous colitis caused by *C. difficile.* The antibodies may also prevent the severity and/or duration of the primary disease, or may prevent the number, duration, and/or the severity of recurrences, or relapses of the disease attributed to the presence of *C. difficile.* The antibodies of the invention may also be useful for diagnosis of an infection by *C. difficile.*

HUMAN ANTIBODIES TO CLOSTRIDIUM DIFFICILE TOXINS

FIELD OF THE INVENTION

[0001] The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind to toxin A and/or toxin B of *Clostridium difficile*, compositions comprising these antibodies and therapeutic methods of using these antibodies.

STATEMENT OF RELATED ART

[0002] *Clostridium difficile* (*C. difficile*) is a gram positive, anaerobic, spore forming bacterium, which is a major cause of hospital-acquired gastrointestinal disease in humans, resulting in symptoms ranging from mild to severe diarrhea and colitis. It is believed that treatment with broad spectrum antibiotics, such as ampicillin, amoxicillin, cephalosporins, fluoroquinolones and clindamycin, may result in disruption of normal intestinal flora, which then allows for colonization of the gut with *C. difficile* (Kelly and Lamont, (1998), Ann. Rev. Med. 49:375-90). Treatment of *C. difficile* infections may involve stopping or modifying the use of broad spectrum antibiotics and requires commencing treatment with specific anticlostridial antibiotics, such as, for example, vancomycin, metronidazole, or fidaxomicin.

[0003] The diarrhea and inflammation observed in patients suffering from a *C. difficile* infection is believed to be due to the production of two toxins by the bacterium, enterotoxin (toxin A) and cytotoxin (toxin B). *C. difficile* toxins A and B are high molecular weight glucosyltransferases that inhibit members of the Rho family of GTPases. Toxin A has a molecular weight of 308 kDa and Toxin B has a molecular weight of 270 kDa. Both toxin A and toxin B deactivate small GTPases such as Rho, Rac and Cdc42 by glucosylation of a threonine residue. Inhibition of these GTPases causes the shutdown of signal transduction cascades leading to: depolymerization of the cytoskeleton, gene transcription of certain stress-activated protein kinases, a drop in synthesis of phosphatidylinositol bisphosphate, and possibly even the loss of cell polarity. Loss of cytoskeletal structure results in cell rounding, and this loss of structure may account for the host reactions to *C. difficile*. Toxin B is at least 1,000 times more cytotoxic than toxin A in cell rounding assays.

[0004] *C. difficile* toxins A and B are 63% homologous in amino acid content and have a similar three-dimensional structure (Davies, AH, (2011), Biochem. J., 436:517-526). The C-terminal third of each toxin is made up of sequences called clostridial repetitive oligopeptides (CROPs), which are highly antigenic. The remaining N-terminal two-thirds of toxins A and B are less similar to each other with respect to sequence homology; however, it is this portion of each protein that contains the glucosyltransferase activity.

[0005] Support for the role of toxin A and/or toxin B in the onset of diarrhea and inflammation following infection with *C. difficile* stems from observations in animal models. For example, oral dosing with the toxins mimics the disease (Kelly and Lamont, (1998), Ann. Rev. Med. 49:375-90). Mutant strains lacking toxin A and B have reduced or altered virulence (Lyras D, O'Connor

JR, Howarth PK *et al.*, *Nature* 458(7242), 1176–1179 (2009); Kuehne SA, Cartman ST, Heap JT, Kelly ML, Cockayne A, Minton NP, *Nature* 15, 467(7316), 711–713 (2010).). Furthermore, administration of polyclonal antibodies to the toxins has been shown to protect hamsters from the disease (Gianasca *et al.,* (1999), Infect. Immun. 66(2): 527-38). In the clinic, studies have shown that there is a correlation between the presence of anti-toxin A or anti-toxin B antibodies and protection against *C. difficile* associated diarrhea and disease recurrence (Warny, M. *et al.,* (1994), Inf. Immun. 62(2): 384-389; Kyne, L. *et al.* (2001), Lancet 357:189-193; Leav, B.A., (2010), Vaccine 28(4):965-969). Development of anti-toxin antibody is associated with asymptomatic carriers (Kyne, L. *et al.* (2000), NEJM 342(6), 390-397). Furthermore, a clinical trial using a combination of *C. difficile* anti-toxin A and anti-toxin B antibodies in conjunction with metronidazole or vancomycin resulted in a reduction in the rate of recurrent infection with *C. difficile* (Lowy, I. *et al.*, (2010), NEJM 362(3):197-205).

[0006] Monoclonal antibodies to *C. difficile* toxin A have been described by Wilkins, *et al.* in US patent 4,879,218. In addition, Rothman *et al*. described a murine monoclonal antibody that cross-reacts with *C. difficile* toxins A and B. Furthermore, Coughlin *et al.* described a monoclonal antibody specific for *C. difficile* toxin B, which did not cross-react with toxin A. Other antibodies to the *C. difficile* toxins have been described (See, for example, US7,151,159; US7,625,559; US8,236,311; US8,257,709; US publication Nos. 2009/0087478; US2010/0233182; US2010/0233181; US2012/0288508; US2012/012160; US2011/0020356; US2012/0121607; EP1766093B1; EP1024826B1; EP1568378A1; EP2305303A2; EP2305293A2; EP2405940A1; EP2261253A2; WO2006/121422; WO2011/130650; WO2010/094970; WO2009/108652; WO2011/063346 and WO2005/058353).

BRIEF SUMMARY OF THE INVENTION

[0007] The invention provides fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that bind specifically to either toxin A or to toxin B produced by *Clostridium difficile (C. difficile)*, or which bind to both toxin A and toxin B of *C. difficile* (*ie.* human monoclonal antibodies that cross react with both toxin A and toxin B). Such antibodies may be useful to neutralize the toxicity associated with either toxin A or toxin B, or both, and as such, may act to lessen the severity of the primary *C. difficile*-associated condition or disease, or reduce the number, the duration, or the severity of disease recurrence, or ameliorate at least one symptom associated with the C. *difficile*-associated condition or disease. Such antibodies may be used alone or in conjunction with a second agent useful for treating a *C. difficile*-associated condition or disease. In certain embodiments, the antibodies specific for toxin A, toxin B, or both, may be given therapeutically in conjunction with a second agent to lessen the severity of the primary *C. difficile*-associated condition or disease, or to reduce the number, the duration, or the severity of disease recurrence, or ameliorate at least one symptom associated with the C. *difficile*-associated condition or disease. In certain embodiments, the antibodies

may be used prophylactically as stand-alone therapy to protect patients who are at risk for developing a *C. difficile*-associated condition or disease. For example, certain patient populations may be at risk for developing a *C. difficile* condition or disease, including elderly patients, or patients who have chronic and/or concomitant underlying medical conditions that may pre-dispose them to a *C. difficile* infection. Other at-risk patient populations include patients who are hospitalized for extended periods of time and who are taking broad spectrum antibiotics that may disrupt the normal intestinal flora and which may predispose them to infection with *C. difficile*. More recent data suggest that patients taking proton pump inhibitors (PPIs) are at risk for developing *C. difficile*-associated diarrhea (Yearsley, K. et al. (2006), Aliment. Pharmacol. Ther. 24(4):613-619; Lowe, DO, et al. Clin. Infect. Dis. (2006), 43(10):1272-1276). Other patient populations at risk for developing a *C. difficile* infection include patients who are undergoing any type of immunosuppressive therapy, such as, but not limited to an anti-cancer drug, general radiotherapy to treat certain cancers, or a drug or drug regimen to prevent tissue or organ graft rejection following a transplant. Patients who receive a hematopoietic stem cell transplant (HSCT) may be at particularly high risk for developing a *C. difficile* infection because of long hospitalizations, receipt of broad-spectrum antibiotics and chemotherapy-related disruption of enteric mucosal barriers (Thibault, A. *et al.*, ((1991), Infect. Control Hosp. Epidemiol. 12:345-8; Anand, A. *et al.* (1993), Clin. Infect. Dis. 17:109-13). Patients who receive a solid organ transplant may also be at risk for developing a *C. difficile* infection. Included in the at-risk population are patients suffering from an autoimmune disease, or patients on dialysis. More recent studies demonstrated that patients who received either an autologous or allogeneic HSCT were not only at greater risk for developing a *C. difficile* infection, but these patients were also at higher risk of developing gastrointestinal graft versus host disease (GI-GVHD) (Alonso, C.D., *et. al.* (2012), Clin Inf. Dis, 54:1053-1063). While this study clearly demonstrated that *C. difficile* infections were a frequent early complication following HSCT, the exact relationship or interplay between *C. difficile* infections (CDI) and GVHD involving the GI tract needs to be explored in greater detail. Any of these patient populations may benefit from treatment with the antibodies of the invention, when given alone or in conjunction with a second agent, such as metronidazole, vancomycin or fidaxomicin.

[0008] The antibodies of the invention can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, *e.g.,* to eliminate residual effector functions (Reddy *et al.,* (2000), J. Immunol. 164:1925-1933).

[0009] Accordingly, in a first aspect, the invention provides an isolated fully human monoclonal antibody or antigen-binding fragment thereof that binds to either toxin A, or to toxin B, or that binds to or cross reacts with both toxin A and toxin B of *Clostridium difficile,* wherein:

a) the isolated antibody or antigen-binding fragment thereof that specifically binds toxin A of *Clostridium difficile* comprises the three heavy chain complementarity determining regions

(HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 98, 114, 130, 146 and 162; and the three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 106, 122, 138, 154 and 170;

b) the isolated antibody or antigen-binding fragment thereof that specifically binds toxin B of *Clostridium difficile* comprises the HCDR1, HCDR2 and HCDR3 contained within a HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and the LCDR1, LCDR2 and LCDR3 contained within a LCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362; and

c) the isolated antibody or antigen-binding fragment that binds to, or cross reacts with both toxin A and toxin B of *Clostridium difficile* comprises the HCDR1, HCDR2 and HCDR3 contained within a HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 34, 50, 66 and 82; and the LCDR1, LCDR2 and LCDR3 contained within a LCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 42, 58, 74 and 90.

[0010] In one embodiment, the human monoclonal antibody that binds to/cross reacts with both toxin A and toxin B of *C. difficile* specifically binds to the carboxy terminal receptor binding domain (CBD) of both toxin A (CBD-A: SEQ ID NO: 375) and toxin B (CBD-B:SEQ ID NO: 376) of *C. difficile*.

[0011] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* binds to toxin A and toxin B with a K_D equal to or less than 10^{-7} M.

[0012] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 18, 34, 50, 66 and 82; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 26, 42, 58, 74 and 90. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, (1997), *J. Mol. Biol. 273*:927-948;

and Martin *et al.*, (1989), *Proc. Natl. Acad. Sci. USA 86*:9268-9272. Public databases are also available for identifying CDR sequences within an antibody.

[0013] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 34, 50, 66 and 82.

[0014] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 42, 58, 74 and 90.

[0015] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises (a) a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 34, 50, 66 and 82; and (b) a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 26, 42, 58, 74 and 90.

[0016] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises :

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 36, 52, 68, and 84, ;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 38, 54, 70 and 86;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 40, 56, 72 and 88;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 44, 60, 76 and 92;

(f) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 46, 62, 78 and 94; and

(g) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 32, 48, 64, 80 and 96.

[0017] In one embodiment, the human antibody or antigen binding fragment thereof that binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 20, 22 and 24, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 28, 30 and 32, respectively.

[0018] In one embodiment, the human antibody or antigen binding fragment thereof that binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 36, 38 and 40, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 44, 46 and 48, respectively.

[0019] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26, 34/42, 50/58, 66/74 and 82/90.

[0020] In one embodiment, the isolated human antibody or antigen-binding fragment thereof which binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 18/26 and 34/42.

[0021] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds to/cross reacts with both toxin A and toxin B binds to:

an epitope within the carboxy terminal receptor binding domain of both toxin A and toxin B of *Clostridium difficile*, wherein the antibody comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26 and 34/42; or

an epitope outside of the carboxy terminal receptor binding domain of both toxin A and toxin B of *Clostridium difficile*, wherein the antibody comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 50/58, 66/74 and 82/90.

[0022] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds to/cross reacts with both toxin A and toxin B of *C. difficile*, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 18, 34, 50, 66 and 82, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 26, 42, 58, 74 and 90, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 24, 40, 56, 72 and 88, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 32, 48, 64, 80 and 96, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 20, 36, 52, 68 and 84, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 22, 38, 54, 70 and 86, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 28, 44, 60, 76 and 92, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected

from the group consisting of SEQ ID NO: 30, 46, 62, 78 and 94, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds to toxin A and to toxin B with a K_D equal to or less than 10^{-9}M.

[0023] In one embodiment, the fully human monoclonal antibody or antigen binding fragment thereof that binds to/cross reacts with both toxin A and toxin B of *C. difficile* comprises a HCDR1 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8$ (SEQ ID NO: 381), wherein X^1 is Gly, X^2 is Phe, Val, or Ile, X^3 is Thr, Ala, or Ser, X^4 is Phe or Leu, X^5 is Ser, Arg, or Asn, X^6 is Gly, Thr, Asp, or Ser, X^7 is His, or Tyr, and X^8 is Gly, or Glu; a HCDR2 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8$ (SEQ ID NO: 382), wherein X^1 is Ile, X^2 is Leu, Ser, or Asp, X^3 is Tyr, Phe, or Ser, X^4 is Asp, or Ser, X^5 is Gly, X^6 is Ser, Gly, Asp, or Thr, X^7 is Ser, His, or Ile, and X^8 is Glu, Gln, or Ile; a HCDR3 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9 – X^{10} – X^{11}$ - $X^{12} – X^{13} – X^{14} – X^{15} – X^{16} – X^{17}$ (SEQ ID NO: 383), wherein X^1 is Ala, or Val, X^2 is Lys, or Arg, X^3 is Gly, or Glu, X^4 is Ser, or Arg, X^5 is Ile, Asp, or Tyr, X^6 is Leu, Ser, or Asp, X^7 is Asn, Ser, Gln, or His, X^8 is Arg, Tyr, or Ser, X^9 is Pro, or Gly, X^{10} is Phe, or Tyr, X^{11} is Asp, Gly, or Tyr, X^{12} is Tyr, X^{13} is Phe, Leu, or absent, X^{14} is Gly, or absent, X^{15} is Met, or absent, X^{16} is Asp, or absent, X^{17} is Val, or absent; a LCDR1 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9 – X^{10} – X^{11}$ - X^{12} (SEQ ID NO: 384), wherein X^1 is Gln, X^2 is Ser, or Glu, X^3 is Ile, Val, or Thr, X^4 is Leu, or Asp, X^5 is Phe, Lys, or Asn, and X^6 is Ser, or Trp, X^7 is Ser, or absent, X^8 is Asn, Asp, or absent, X^9 is Asn, or absent, X^{10} is Lys, or absent, X^{11} Ile, Asn, or absent, X^{12} is Tyr, or absent; a LCDR2 sequence comprising the formula $X^1 – X^2 – X^3$ (SEQ ID NO: 385), wherein X^1 is Trp, Lys, or Arg, X^2 is Ala or Thr, and X^3 is Ser; and a LCDR3 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9$ (SEQ ID NO: 386), wherein X^1 is Gln or His, X^2 is Gln, or Glu, X^3 is Tyr, X^4 is Tyr, or Asn, X^5 is Thr, or Ser, X^6 is Leu, Ala, or Tyr, X^7 is Pro, Phe, or Ser, X^8 is Leu, Phe, or Arg and X^9 is Thr, or Ala.

[0024] In one embodiment, the invention provides an isolated human monoclonal antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, wherein the antibody comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the HCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 2, 98, 114, 130, 146 and 162; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the LCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 10, 106, 122, 138, 154 and 170.

[0025] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 98, 114, 130, 146 and 162.

[0026] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 106, 122, 138, 154 and 170.

[0027] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, comprises (a) a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 98, 114, 130, 146 and 162; and (b) a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 106, 122, 138, 154 and 170.

[0028] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 100, 116, 132, 148 and 164;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 102, 118, 134, 150 and 166;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 104, 120, 136, 152 and 168;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 108, 124, 140, 156, and 172;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 110, 126, 142, 158 and 174; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 112, 128, 144, 160 and 176.

[0029] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 148, 150 and 152, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 156, 158 and 160, respectively.

[0030] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 98/106, 114/122, 130/138, 146/154 and 162/170.

[0031] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*, comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 146/154.

[0032] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile* binds to:

an epitope within the carboxy terminal receptor binding domain of toxin A of *Clostridium difficile*, wherein the antibody comprises a HCVR/LCVR amino acid sequence pair

selected from the group consisting of SEQ ID NOs: 2/10, 98/106, 130/138, 146/154 and 162/170; or

an epitope outside of the carboxy terminal receptor binding domain of toxin A of *Clostridium difficile*, wherein the antibody comprises a HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 114/122.

[0033] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to toxin A of *C. difficile*, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 98,114,130,146 and 162, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 106, 122, 138, 154 and 170, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 104,120,136,152 and 168, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 112, 128, 144, 160 and 176, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 100, 116, 132, 148 and 164, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 102, 118, 134, 150 and 166, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 108, 124, 140, 156 and 172, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 110, 126, 142, 158 and 174, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) demonstrates a K_D equal to or less than 10^{-9}M; (vi) demonstrates neutralization of Toxin A (at a concentration of 32pM) with an IC50 ranging from about 7pM to about 65pM in a cell viability assay.

[0034] In one embodiment, the fully human monoclonal antibody or antigen binding fragment thereof that binds specifically to toxin A of *C. difficile* comprises a HCDR1 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8$ (SEQ ID NO: 387), wherein X^1 is Gly, or Arg, X^2 is Phe, X^3 is Asn, or Thr, X^4 is Phe, X^5 is Gly, Ser, Asn, or Thr, X^6 is Thr, Ser, Asn, or Asp, X^7 is His, Tyr, or Phe and X^8 is Asp, Val, Ala, or Tyr; a HCDR2 sequence comprising the formula

$X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8$ (SEQ ID NO: 388), wherein X^1 is Leu, or Ile, X^2 is Thr, Gly, Ser, or Trp, X^3 is Ser, Thr, Gly, or Phe, X^4 is Thr, Val, Tyr, Val, Asp, or Gly, X^5 is Gly, X^6 is Gly, Asp, Ser, or Ala, X^7 is Ser, Thr, Asn, or Ala, and X^8 is Ala, Thr, Glu, Lys, or absent; a HCDR3 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9 – X^{10} – X^{11}$ - $X^{12} – X^{13} – X^{14} – X^{15} – X^{16} – X^{17}– X^{18}$ - $X^{19} – X^{20} – X^{21} – X^{22} – X^{23} – X^{24}$ (SEQ ID NO: 389), wherein X^1 is Ala, X^2 is Lys, or Arg, X^3 is Thr, Asp, or Ser, X^4 is Phe, Arg, His, Ala, or Leu, X^5 is Asn, Gly, or Lys, X^6 is Trp, Gly, Asp, or Ile, X^7 is Asn, Ala, or Phe, X^8 is Ser, Asn, Tyr, Gly, or Asp, X^9 is Tyr, Ile, Ala, Thr, Glu, or Leu, X^{10} is Phe, Tyr, Ser, Gly, or absent, X^{11} is Asp. Ser, Gly, or absent, X^{12} is Tyr, Phe, Ser, Pro, or absent, X^{13} is Tyr, Leu, or absent, X^{14} is Tyr, Phe, or absent, X^{15} Gly, Asn, Asp, or absent, X^{16} is Met, Arg, Tyr, or absent, X^{17} is Asp, or absent, X^{18} is Tyr, Val, or absent, X^{19} is Tyr, or absent, X^{20} is Tyr, or absent, X^{21} is Gly, or absent, X^{22} is Met, or absent, X^{23} is Asp, or absent, X^{24} is Val, or absent; a LCDR1 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7$ (SEQ ID NO: 390), wherein X^1 is Gln, X^2 is Ser, Asp, or Thr, X^3 is Ile, or Val, X^4 is Ser, X^5 is Thr, Asn, or Ser, X^6 is Tyr, Trp, Phe, or Ser and X^7 is Tyr, or absent; a LCDR2 sequence comprising the formula $X^1 – X^2 – X^3$ (SEQ ID NO: 391), wherein X^1 is Gly, Ala, Lys, or Thr, X^2 is Ala, Thr, or Val and X^3 is Ser; and a LCDR3 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9 – X^{10}$ (SEQ ID NO: 392), wherein X^1 is Gln or absent, X^2 is Gln, Lys, or absent, X^3 is Tyr, Asn, or absent, X^4 is Gly, Asn, Thr, Tyr, His, or absent, X^5 is Asn, Ser, or absent, X^6 is Ser, Ala, Tyr, Asp, Trp, or absent, X^7 is Leu, Pro, Ser, or absent, X^8 is Tyr, Phe, Arg, Pro, or absent, X^9 is Thr, Tyr, or absent, and X^{10} is Thr.

[0035] In one embodiment, the invention provides an isolated human monoclonal antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile*, wherein the antibody comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the HCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the LCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

[0036] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile* comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354.

[0037] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile* comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

[0038] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile* comprises (a) a HCVR having an amino

acid sequence selected from the group consisting of SEQ ID NOs: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and (b) a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

[0039] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile* comprises

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340 and 356;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342 and 358;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344 and 360;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348 and 364;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350 and 366; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352 and 368.

[0040] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile*, comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NO: 276, 278 and 280, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NO: 284, 286 and 288, respectively.

[0041] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile* comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362.

[0042] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile* comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282.

[0043] In one embodiment, the isolated human antibody or antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile* binds to:

an epitope within the carboxy terminal receptor binding domain of toxin B of *Clostridium difficile*, wherein the antibody comprises a HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 178/186; or

an epitope outside of the carboxy terminal receptor binding domain of toxin B of *Clostridium difficile*, wherein the antibody comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 194/202, 210/218, 226/234, 242/250, 258/266, 274/282 and 290/298.

[0044] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to toxin B of *C. difficile*, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO:186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO:184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344 and 360, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO:192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352 and 368, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 180,196, 212, 228, 244, 260, 276, 292, 308, 324, 340 and 356, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342 and 358, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348 and 364, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350 and 366, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) demonstrates a K_D equal to or less than 10^{-9}M; (vi) demonstrates neutralization of Toxin B (at a concentration of 0.03pM) with an IC50 ranging from about 25pM to about 320pM in a cell viability assay.

[0045] In one embodiment, the fully human monoclonal antibody or antigen binding fragment thereof that binds specifically to toxin B of *C. difficile* comprises a HCDR1 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9 – X^{10}$ (SEQ ID NO: 393), wherein X^1 is Gly, X^2 is Phe, Asp, or Tyr, X^3 is Thr, Asn, Ser, or Val, X^4 is Phe, or Val, X^5 is Ser, Arg, Lys, Glu, or Thr, X^6 is Ser, Ile, Asp, or Arg, X^7 is Phe, Tyr, or Asn, X^8 is Gly, Ala, Ser, or Tyr; X^9 is Ala, or absent and X^{10} is Ala or absent; a HCDR2 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9$ (SEQ ID NO: 394), wherein X^1 is Ile, or Thr, X^2 is Ser, Gly, Tyr, or Asn,

X^3 is Thr, Gly, Tyr, Trp, Pro, or Ser, X^4 is Asp, Ser, Asn, Arg, Lys, or Asp, X^5 is Gly, Ser, or Thr, X^6 is Ser, Asp, Gly, Lys, or Asn, X^7 is Lys, Arg, Asn, Ser, Trp, or Gly, X^8 is Lys, Thr, Ile, or Tyr, X^9 is His, or absent; a HCDR3 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9 – X^{10} – X^{11}$ - $X^{12} – X^{13} – X^{14} – X^{15} – X^{16}$ (SEQ ID NO: 395), wherein X^1 is Ala, or Val, X^2 is Arg, Lys, Thr, or Ser, X^3 is Val, Gly, Asp, Arg, or Tyr, X^4 is Gly, Trp, Arg, Lys, or Asn, X^5 is Glu, Tyr, Arg, Ser, or Trp, X^6 is Leu, Tyr, Ser, Pro, or Asn, X^7 Leu, Asp, Tyr, Ser, or Asp, X^8 is Asn, Ser, Phe, Lys, Arg, Asp, or Gly, X^9 is Tyr, Gly, Phe, Asp, Trp, or Val, X^{10} is Ser, Tyr, Asn, Asp, or absent, X^{11} is Tyr, Leu, Val, Gly, or absent, X^{12} is Tyr, Leu, Phe, Val, or absent, X^{13} is Asn, Gly, Asp, Phe, or absent, X^{14} is Tyr, Met, Asp, or absent, X^{15} Asp, Tyr, or absent, and X^{16} is Val, or absent; a LCDR1 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7$ (SEQ ID NO: 396), wherein X^1 is Gln, Leu, or Arg, X^2 is Gly, Asp, or Ser, X^3 is Ile, or Val, X^4 is Arg, Ser, Gly, or Tyr, X^5 is Ser, or Asn, X^6 is Trp, His, Asn, Phe, Ser, or Asp, and X^7 is Tyr, or absent; a LCDR2 sequence comprising the formula $X^1 – X^2 – X^3$ (SEQ ID NO: 397), wherein X^1 is Ala, Ser, Asp, or Gly, X^2 is Ala, or Thr, and X^3 is Ser; and a LCDR3 sequence comprising the formula $X^1 – X^2 – X^3 – X^4 – X^5 – X^6 – X^7 – X^8 – X^9$ (SEQ ID NO: 398), wherein X^1 is Gln, His, or Leu, X^2 is Gln, X^3 is Ala, Tyr, Arg, Asp, His, or Val, X^4 is Tyr, Gly, Asn, Ser, Ile, or Lys, X^5 is Ser, Leu, Pro, Ile, Asn, Thr, or Gly, X^6 is Phe, Tyr, Trp, or Ser, X^7 is Pro, X^8 is Leu, Pro, Phe, Val, or Tyr and X^9 is Thr.

[0046] In one embodiment, the invention provides an isolated antibody or antigen-binding fragment thereof that competes for specific binding to *C. difficile* toxin A and/or toxin B with an antibody or antigen-binding fragment comprising the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

[0047] In a related embodiment, the invention provides an isolated antibody or antigen-binding fragment thereof that competes for specific binding to *C. difficile* toxin A and/or toxin B with an antibody or antigen-binding fragment comprising the heavy and light chain CDRs contained within heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 18/26, 34/42, 146/154 and 274/282.

[0048] In one embodiment, the invention provides an isolated antibody or antigen-binding fragment thereof that binds the same epitope on *C. difficile* toxin A and/or toxin B as an antibody or antigen-binding fragment comprising the CDRs of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and the CDRs of a light chain variable region (LCVR), wherein the

LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

[0049] In a related embodiment, the invention provides an isolated antibody or antigen-binding fragment thereof that binds the same epitope on *C. difficile* toxin A and/or toxin B as an antibody or antigen-binding fragment comprising the heavy and light chain CDRs contained within heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 18/26, 34/42, 146/154, 274/282.

[0050] In certain embodiments of the invention, the antibodies may interact with, or bind to, amino acid residues 468-863 of the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, the sequence of which is shown in SEQ ID NO: 375. This region corresponds to amino acid residues ranging from residues 2315-2710 of SEQ ID NO: 378 (full length toxin A). In certain embodiments of the invention, the antibodies may interact with, or bind to, an epitope in the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, wherein the epitope is selected from the group consisting of residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610 of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 375, residues 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375. These residues correspond to the amino acid sequences found in the full length toxin A sequence having SEQ ID NO: 378, with the particular regions identified as residues 2315-2335 of SEQ ID NO: 378, residues 2357-2377 of SEQ ID NO: 378, residues 2449-2457 of SEQ ID NO: 378, residues 2491-2550 of SEQ ID NO: 378, residues 2571-2641 of SEQ ID NO: 378, residues 2646-2661 of SEQ ID NO: 378 and residues 2705-2710 of SEQ ID NO: 378. In one embodiment, the antibody that binds to or interacts with an epitope in the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, selected from the group consisting of residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610 of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 375, residues 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375 comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 146/154. In one embodiment, the antibody that binds to or interacts with an epitope in the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, selected from the group consisting of residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610 of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 375, residues 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375 is combined with a second antibody that binds specifically to toxin B of *Clostridium difficile* in a pharmaceutical composition. In one embodiment, this second antibody that interacts with or binds to toxin B of *Clostridium difficile* comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282.

[0051] In a second aspect, the invention provides nucleic acid molecules encoding anti-toxin A and/or anti-toxin B antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0052] In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337 and 353 or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0053] In one embodiment, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 17, 33, 145 and 273.

[0054] In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345 and 361, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0055] In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 25, 41, 153 and 281.

[0056] In one embodiment, the invention also provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 23, 39, 55, 71, 87, 103, 119, 135, 151, 167, 183, 199, 215, 231, 247, 263, 279, 295, 311, 327, 343 and 359 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 31, 47, 63, 79, 95, 111, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, 287, 303, 319, 335, 351 and 367, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0057] In one embodiment, the invention provides an antibody or fragment thereof further comprising a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, 339 and 355, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 293, 309, 325, 341 and 357, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain encoded by a nucleotide sequence

selected from the group consisting of SEQ ID NO: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347 and 363, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, 349 and 365, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0058] In a third aspect, the invention features a human antibody or antigen-binding fragment specific for toxin A and/or toxin B of *C. difficile* comprising a HCVR encoded by nucleotide sequence segments derived from V_H, D_H and J_H germline sequences, and a LCVR encoded by nucleotide sequence segments derived from V_K and J_K germline sequences, with combinations as shown in Table 2.

[0059] The invention encompasses antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al.* (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0060] In a fourth aspect, the invention provides a pharmaceutical composition comprising at least one isolated fully human monoclonal antibody or antigen-binding fragment thereof that binds to either toxin A or toxin B of *C. difficile*, or that binds to both toxin A and toxin B of *C. difficile* and a pharmaceutically acceptable carrier or diluent. In one embodiment, the invention provides a pharmaceutical composition comprising an isolated fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to only toxin A of *C. difficile* and a pharmaceutically acceptable carrier or diluent. In one embodiment, the invention provides a pharmaceutical composition comprising an isolated fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to only toxin B of *C. difficile* and a pharmaceutically acceptable carrier or diluent. In one embodiment, the invention provides a pharmaceutical composition comprising two fully human monoclonal antibodies or antigen-binding fragments thereof, one that binds specifically to toxin A and one that binds specifically to toxin B of *C. difficile* and a pharmaceutically acceptable carrier or diluent. In one embodiment, the invention provides a pharmaceutical composition comprising one dual binding fully human monoclonal antibody (an antibody that binds to both toxin A and toxin B) and a pharmaceutically acceptable carrier or diluent. In one embodiment, the invention provides a pharmaceutical composition comprising two dual binding fully human monoclonal antibodies (an antibody that binds to both toxin A and toxin B) and a pharmaceutically acceptable carrier or diluent. The dual antibodies used in the pharmaceutical composition may recognize and/or bind to the same epitope on toxin A or toxin B, or may recognize and/or bind to different epitopes on toxin A or toxin B. It is to be understood that any combination of antibodies as described herein

may be used in a pharmaceutical composition to achieve the desired results in the patient population in need of such therapy. For example, two antibodies that recognize and/or bind only toxin A may be used in a composition. Alternatively, two antibodies that recognize and/or bind only toxin B may be used in a composition. In one embodiment, one antibody that recognizes/binds to only toxin A or toxin B may be combined with a dual binding antibody in a composition. In one embodiment, one antibody that recognizes/binds to only toxin A may be combined with one antibody that recognizes/binds to only toxin B and this combination may be used in a composition.

[0061] In one embodiment, the pharmaceutical composition comprises a fully human monoclonal antibody that binds to the carboxy terminal receptor binding domain of both toxin A and toxin B of *C. difficile* having any one or more of the characteristics described herein. The antibody that binds to the carboxy terminal receptor binding domain of both toxin A and toxin B of *C. difficile* binds toxin A and toxin B with a K_D equal to or less than 10^{-7}M.

[0062] In one embodiment, the composition comprises an antibody that binds both toxin A and toxin B of *C. difficile* and has a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26, 34/42, 50/58, 66/74 and 82/90.

[0063] In one embodiment, the composition comprises an antibody that binds both toxin A and toxin B of *C. difficile* and has a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26 and 34/42.

[0064] In one embodiment, the pharmaceutical composition comprises at least one antibody that binds a *Clostridium difficile* toxin, wherein the antibody is selected from:

a) an isolated antibody or antigen-binding fragment thereof that specifically binds toxin A of *Clostridium difficile*, wherein the antibody comprises the three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 2, 98, 114, 130, 146 and 162; and the three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 10, 106, 122, 138, 154 and 170;

b) an isolated antibody or antigen-binding fragment thereof that specifically binds toxin B of *Clostridium difficile*, wherein the antibody comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the HCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the LCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362; and

c) an isolated antibody or antigen-binding fragment that binds to/cross reacts with both toxin A and toxin B of *Clostridium difficile*, wherein the antibody comprises the three heavy

chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the HCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 18, 34, 50, 66 and 82; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the LCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 26, 42, 58, 74 and 90.

[0065] In one embodiment, the pharmaceutical composition comprises an isolated first fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds toxin A of *Clostridium difficile,* as described herein, and an isolated second fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds toxin B of *Clostridium difficile*, as described herein, and a pharmaceutically acceptable carrier or diluent.

[0066] In one embodiment, the composition comprises at least one antibody, or an antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile* and at least one antibody, or an antigen-binding fragment thereof that binds specifically to toxin B of *Clostridium difficile*, wherein:

a) the antibody or antigen-binding fragment thereof that binds specifically to toxin A comprises the three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 2, 98, 114, 130, 146 and 162; and the three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 10, 106, 122, 138, 154 and 170; and wherein

b) the antibody or antigen-binding fragment thereof that binds specifically to toxin B comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the HCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the LCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

[0067] In one embodiment, the pharmaceutical composition comprises:

a) an isolated first fully human monoclonal antibody, or antigen-binding fragment thereof that specifically binds toxin A of *Clostridium difficile*, which comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 98, 114, 130, 146 and 162; and a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 106, 122, 138, 154 and 170; and

b) an isolated second fully human monoclonal antibody, or antigen-binding fragment thereof that specifically binds toxin B of *Clostridium difficile*, which comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 178, 194, 210,

226, 242, 258, 274, 290, 306, 322, 338 and 354; and a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

[0068] In one embodiment, the pharmaceutical composition comprises an isolated first fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds toxin A of *C. difficile*, which comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 98/106, 114/122, 130/138, 146/154 and 162/170; and an isolated second fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds toxin B of *C. difficile*, which comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362.

[0069] In another embodiment, the pharmaceutical composition comprises an isolated first fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds toxin A of *C. difficile*, which comprises a HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 146/154; and an isolated second fully human antibody or antigen-binding fragment thereof that specifically binds toxin B of *C. difficile*, which comprises a HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282.

[0070] In another related embodiment, the pharmaceutical composition comprises:

a) an isolated first human antibody, or antigen-binding fragment thereof that specifically binds toxin A of *Clostridium difficile*, comprising a HCDR1 having the amino acid sequence of SEQ ID NO: 148, a HCDR2 having the amino acid sequence of SEQ ID NO: 150, a HCDR3 having the amino acid sequence of SEQ ID NO: 152, a LCDR1 having the amino acid sequence of SEQ ID NO: 156, a LCDR2 having the amino acid sequence of SEQ ID NO: 158, a LCDR3 having the amino acid sequence of SEQ ID NO: 160;

b) an isolated second human antibody, or antigen-binding fragment thereof that specifically binds toxin B of *Clostridium difficile*, comprising a HCDR1 having the amino acid sequence of SEQ ID NO: 276, a HCDR2 having the amino acid sequence of SEQ ID NO: 278, a HCDR3 having the amino acid sequence of SEQ ID NO: 280, a LCDR1 having the amino acid sequence of SEQ ID NO: 284, a LCDR2 having the amino acid sequence of SEQ ID NO: 286, a LCDR3 having the amino acid sequence of SEQ ID NO: 288; and

c) a pharmaceutically acceptable carrier or diluent.

[0071] In one embodiment, the antibodies of the invention, or compositions containing one or more antibodies of the invention may be used to neutralize either toxin A, or toxin B, or both toxin A and B from any strain of *Clostridium difficile*.

[0072] In one embodiment, the antibodies of the invention, or compositions containing one or more antibodies of the invention may be used to neutralize toxins A and/or B from a hypervirulent strain of *Clostridium difficile*.

[0073] In one embodiment, the antibodies of the invention, or compositions containing one or more antibodies of the invention may be used to neutralize toxins A and/or B from a BI/NAP1/027 strain.

[0074] In one embodiment, the antibodies of the invention, or compositions containing one or more antibodies of the invention, may be used to neutralize toxins A and/or B from a BI/NAP1/027 strain, wherein the BI/NAP1/027 strain is selected from the group consisting of VA5, VA17, 6336 and 6443.

[0075] In one embodiment, the antibody composition comprising a first antibody that binds specifically to toxin A, may be administered alone as a separate composition and the antibody composition comprising the second antibody that binds specifically to toxin B may also be administered as a separate composition. Each composition may be prepared for delivery to the patient in separate syringes, or delivery devices, or vials. When formulated separately as two compositions, both compositions may be delivered separately, with one antibody composition being given immediately prior to the other antibody composition. Alternatively, the two antibody compositions may be mixed together shortly before administration and given concurrently.

[0076] In one embodiment, the invention features a composition, which is a combination of an antibody or antigen-binding fragment of an antibody of the invention, and a second therapeutic agent.

[0077] The second therapeutic agent may be a small molecule drug, a protein/polypeptide, an antibody, a nucleic acid molecule, such as an anti-sense molecule, or a siRNA. The second therapeutic agent may be synthetic or naturally derived.

[0078] The second therapeutic agent may be any agent that is advantageously combined with the antibody or fragment thereof of the invention, for example, a probiotic, an antibiotic, a toxoid, a vaccine specific for *C. difficile*, or a second different antibody against *C. difficile* toxin A and/or toxin B.

[0079] In certain embodiments, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with the antibody or antigen-binding fragment of an antibody of the invention, if such side effect(s) should occur.

[0080] It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (*e.g.,* control of any adverse effects). As used herein, additional

therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

[0081] When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art.

[0082] A fifth aspect of the invention provides a method for treating a patient suffering from a *Clostridium difficile*-associated condition or disease, or for treating at least one symptom or complication associated with the condition or disease, or for preventing the development of a *Clostridium difficile*-associated condition or disease in a patient at risk thereof, the method comprising administering to the patient an effective amount of an antibody or an antigen-binding fragment thereof that binds to *C. difficile* toxin A and/or toxin B; or a pharmaceutical composition comprising an effective amount of an antibody or an antigen-binding fragment thereof that binds to *Clostridium difficile* toxin A and/or toxin B, such that the *Clostridium difficile*-associated condition or disease is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the condition or disease is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of recurrences, or relapses with *Clostridium difficile* is reduced.

[0083] In one embodiment, the invention provides for use of one or more antibodies of the invention, or pharmaceutical compositions comprising one or more antibodies of the invention in the manufacture of a medicament for use in treating a patient suffering from a *Clostridium difficile*-associated condition or disease, or for treating at least one symptom or complication associated with the condition or disease, or for preventing the development of a *Clostridium difficile*-associated condition or disease in a patient at risk thereof, wherein the *Clostridium difficile*-associated condition or disease is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the condition or disease is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of recurrences, or relapses with *Clostridium difficile* is reduced. The at least one symptom or complication associated with the *Clostridium difficile*-associated condition or disease may be selected from the group consisting of anorexia, abdominal pain, abdominal bloating, diarrhea with or without bleeding, dehydration, malnutrition, pseudomembranous colitis, complete or segmental colonic resection, fever and systemic infection (sepsis), death, relapse of the *Clostridium difficile* condition or disease, and rejection of a transplanted tissue or organ.

[0084] In one embodiment, the patient to be treated with the antibodies of the invention, or with the pharmaceutical compositions comprising one or more antibodies of the invention are infected with a hypervirulent isolate of *Clostridium difficile*, such as one belonging to the BI/NAP1/027 group, or may be at risk for developing an infection with a hypervirulent strain, as described herein.

[0085] In a related embodiment, the antibodies of the invention, or a pharmaceutical composition containing one or more antibodies of the invention may be used to neutralize the

toxins produced by a hypervirulent strain of *Clostridium difficile*, such as but not limited to any of those belonging to the BI/NAP1/027 group of strains. Included in these hypervirulent strains are clinical isolates noted herein as VA5, VA17, 6336 and 6443, described herein in Example 10.

[0086] In one embodiment, the patient at risk of developing a *Clostridium difficile*-associated condition or disease, who may benefit from treatment with the antibodies of the invention, or with a composition comprising one or more antibodies of the invention, may be selected from an elderly (≥ 65 years old) patient, a patient who is immunocompromised due to underlying illness or due to administration of immunosuppressive therapeutics, a patient who has some underlying medical condition that may pre-dispose them to acquiring a *Clostridium difficile* infection, a patient hospitalized for an extended period of time (one week or more), a patient who has been treated for an extended period of time (≥ 14 days) with broad spectrum antibiotics, a cancer patient, a transplant patient, and a patient on therapy with agents such as but not limited to a proton pump inhibitor, or histamine H2 receptor inhibitor that are used for treatment of gastrointestinal diseases or conditions to reduce or treat gastric acidity, gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, or heartburn.

[0087] In one embodiment, the patient at risk of developing a *Clostridium difficile*-associated condition or disease is a cancer patient. In a related embodiment, the cancer patient is undergoing treatment with an anti-cancer drug, or undergoing radiotherapy to treat a cancer.

[0088] In one embodiment, the patient at risk of developing a *Clostridium difficile*-associated condition or disease is a transplant patient. In a related embodiment, the transplant patient is a patient receiving a hematopoietic stem cell transplant, or a solid tissue or organ transplant. In certain embodiments, the transplant patient is being treated with an immunosuppressive drug, or any transplant rejection drug, or is a patient who is undergoing treatment with a drug regimen to prevent tissue or organ graft rejection following the transplant.

[0089] In one embodiment, the antibody is administered therapeutically (administered after the infection has been established and given throughout the course of the infection) to a patient suffering from a *Clostridium difficile*-associated condition or disease, or suffering from at least one symptom or complication associated with the condition or disease. In one embodiment, the antibody is administered prophylactically (administered prior to development of the infection) to a patient at risk for developing a *Clostridium difficile*-associated condition or disease, or at risk for developing at least one symptom or complication associated with the *Clostridium difficile* condition or disease. For example, such "patients at risk for developing a *Clostridium difficile* infection" include the elderly (65 years of age or older), or patients who may be immunocompromised due to illness or due to administration of immunosuppressive therapeutics, or patients who have some underlying medical condition that may pre-dispose them to acquiring a *Clostridium difficile* infection, or patients hospitalized for long periods of time (generally one week or longer), or patients who have been treated for a long period of time with

broad spectrum antibiotics (generally 14 days or longer), or patients on therapy with proton pump inhibitors for treatment of gastrointestinal diseases or conditions. Other patients at risk for developing a *Clostridium difficile* infection are those patients that are in need of a tissue or organ transplant, who would be undergoing treatment with immunosuppressive drugs to prevent tissue or organ rejection. This patient population includes individuals in need of either an autologous or allogeneic hematopoietic stem cell transplant. The long hospitalization required for these patients, in addition to receipt of high doses of antibiotic therapy to prevent other types of infections may pre-dispose these patients to acquiring a primary *C. difficile* infection. Alternatively, if a patient in need of such a transplant already suffers from a *C. difficile* infection, or has exhibited symptoms of a *C. difficile* infection, that patient may be prone to a recurrence, or exacerbation of such infection when placed on high dose antibiotic therapy, then followed by immunosuppressive therapy to prevent graft rejection. Furthermore, these transplant patients may be at risk not only for acquiring a *C. difficile* infection, but also may be at risk for rejection of the transplant due to GI related graft versus host disease (GI-GVHD), which appears to be enhanced in transplant patients suffering from infection with *C. difficile* (See Alonso, C.D. *et.al.,* (2012), Clin. Infect. Dis. 54, 1053–1063. The relationship between *C. difficile* infection and GVHD involving the GI tract is unclear at this time, but it is appears that this patient population would benefit from therapy with the anti-toxin A and/or anti-toxin B antibodies of the invention. While it is envisioned that this patient population may be treated therapeutically (after the start of the infection), it is also contemplated that these patients would benefit from prophylactic (prior to infection) administration of any of the antibodies of the invention. The patients who are candidates for treatment with the antibodies of the invention may be administered the compositions comprising one or more antibodies by any route of delivery suitable for administration, including but not limited to intravenous injection, or subcutaneous injection.

[0090] In one embodiment, the pharmaceutical composition comprising the antibodies of the invention is administered to the patient in combination with one or more therapeutic agents useful for treating a *C. difficile* infection.

[0091] In one embodiment, the one or more therapeutic agents may be selected from the group consisting of a toxoid, a probiotic, a *C. difficile* vaccine (*e.g.*, inactivated toxins A and B, such as, but not limited to ACAM-CDIFF™), an antibiotic (e.g. metronidazole, vancomycin or fidaxomicin), another different antibody to *C. difficile* toxin A and/or B, and any other palliative therapy useful for reducing the severity of the *C. difficile* disease or for reducing the frequency of recurrence of the *C. difficile* disease or for ameliorating at least one symptom associated with a *C. difficile*-associated condition or disease.

[0092] In another embodiment, the one symptom or complication associated with the *C. difficile*-associated condition or disease is selected from the group consisting of diarrhea,

pseudomembranous colitis, relapse/recurrence of the *Clostridium difficile* condition or disease, and rejection of a transplanted tissue or organ.

[0093] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0094] Figure 1 shows the domain structures of Toxin A and Toxin B from *Clostridium difficile* (See Davies AH, *et al.,* Biochem. J. (2011), 436:517-526).

[0095] Figure 2 is a graph showing results of hamster relapse assays as the percentage of hamsters surviving clindamycin and vancomycin treatment following *C. difficile* challenge and the effect of treatment with anti-toxin A and anti-toxin B mAbs. All antibodies were given subcutaneously once a day on days 3-6. Positive control antibodies are comparator antibodies, anti-Toxin A (control I) and anti-Toxin B (control II). Vancomycin was given as an oral dose at 10 mg/kg on days 1-3 to all animals. (● with dotted line: PBS control; △ with dotted line: Negative isotype control at 10 mg/kg; □ with solid line: Control I/Control II at 5 mg/kg each (5/5): ◆ with solid line: H1H3330P/H1H3347P at 5 mg/kg each (5/5)).

[0096] Figure 3 is a graph showing results of hamster relapse assays as the percentage of hamsters surviving clindamycin and vancomycin treatment following *C. difficile* challenge and the effect of anti-toxin A and anti-toxin B mAbs. All antibodies were given subcutaneously once on day 3. Positive control antibodies are comparator antibodies, anti-Toxin A (control I) and anti-Toxin B (control II). Vancomycin was given as an oral dose at 10 mg/kg on days 1-3 to all animals. (△ with dotted line: Negative isotype control at 10 mg/kg; □ with solid line: Control I/Control II at 5 mg/kg each (5/5); ◆ with solid line: H1H3330P/H1H3347P at 5 mg/kg each (5/5); O with solid line: Control I/Control II at 2 mg/kg each (2/2); ⬡ with solid line: H1H3330P/H1H3347P at 2 mg/kg each (2/2)).

[0097] Figure 4 is a graph showing survival results in an acute model of *C. difficile* infection in hamsters. Results are shown as the percentage of hamsters surviving *C. difficile* challenge (day 0) following clindamycin treatment (day -1). All antibodies were given subcutaneously on each of 4 days from day -3 to day 0. Antibodies were administered at 50 mg/kg each (50/50), 16.6 mg/kg each (16.6/16.6), 5.5 mg/kg each (5.5/5.5) and 1.85 mg/kg each (1.85/1.85). (▽ with solid line: Uninfected; ● with dotted line: PBS control; △ with dotted line: Negative isotype control at 100 mg/kg; ◆ with solid line: H1H3330P/H1H3347P at 50 mg/kg each (50/50); O with solid line: H1H3330P/H1H3347P at 16.6 mg/kg each (16.6/16.6); □ with solid line: H1H3330P/H1H3347P at 5.5 mg/kg each (5.5/5.5); ┼ with a solid line: H1H3330P/H1H3347P at 1.85 mg/kg each (1.85/1.85).

[0098] Figure 5 is a graph showing survival results in an acute model of *C. difficile* infection in hamsters. Results are shown as the percentage of hamsters surviving *C. difficile* challenge (day 0) following clindamycin treatment (day -1). All antibodies were given subcutaneously on each

of 4 days from day -3 to day 0. Antibodies were administered at 20 mg/kg each (20/20), or at 5 mg/kg each (5/5). (▽ with solid line: Uninfected; ● with dotted line: PBS control; △ with dotted line: Negative isotype control at 40 mg/kg; □ with solid line: Control I/Control II at 20 mg/kg each (20/20); ⊠ with solid line: Control I/Control II at 5 mg/kg each (5/5); ◆ with solid line: H1H3330P/H1H3347P at 20 mg/kg each (20/20); ◊ with solid line: H1H3330P/H1H3347P at 5 mg/kg each (5/5)).

DETAILED DESCRIPTION

[0099] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0100] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described.

Definitions

[0101] The term "toxin A" (also referred to as "tcdA") refers to the toxin A protein produced by *Clostridium difficile* (also referred to herein as "*C. difficile*"). The amino acid sequence of "toxin A' is provided in GenBank as accession number CAA63564 and is also referred to herein as SEQ ID NO: 378. Toxin A is encoded by the nucleic acid provided herein as SEQ ID NO: 377, and is also found in GenBank as accession number AM180355.

[0102] The term "toxin B" (also referred to as "tcdB") refers to the toxin B protein produced by *Clostridium difficile*. The amino acid sequence of "toxin B' is provided in GenBank as accession number CAJ67492 and is also referred to herein as SEQ ID NO: 380. Toxin B is encoded by the nucleic acid provided herein as SEQ ID NO: 379, and is also found in GenBank as accession number AM180355.

[0103] The "carboxy terminal receptor binding domain of toxin A and toxin B of *Clostridium difficile*" refers to the portion of toxin A and toxin B from *C. difficile* that is responsible for binding to the target cell, thus allowing for subsequent receptor mediated endocytosis. As described herein, the amino acid sequence of the carboxy terminal receptor binding domain of toxin A is shown in SEQ ID NO: 375. The amino acid sequence of the carboxy terminal receptor binding domain of toxin B is shown in SEQ ID NO: 376. The various domains of toxin A and toxin B from *C. difficile* are illustrated in Figure 1 and further described in Davies *et al.* (Davies, AH, *et al.*, Biochem. J. (2011), 436:517-526).

[0104] The "BI/NAP1/027" designation for *Clostridium difficile* refers to a highly virulent group

of isolates of *Clostridium difficile* that has been associated with an increase in morbidity and mortality throughout Europe and North America (Loo, VG, *et al.*, (2005), N Engl J Med, 353:2442-9; McDonald, LC *et al.* (2006), Emerg Infect Dis, 12:409-15; McDonald, LC, *et al.*,(2005), N Engl J Med, 353:2433-41; Redelings, MD, *et al.*, (2007), Emerg Infect Dis 13:1417-9). The "BI/NAP1/027" designation further refers to North American pulsed-field type I (NAP1), ribotype 027, and group BI by restriction endonuclease analysis. It was originally identified in the 1980s, but was not originally identified as being resistant to the newer fluoroquinolone agents and was not epidemic prior to 2000 (Warny, M. et al., (2005), Lancet 366:1079-84; Kelly, CP, et al., N Engl J Med 359:1932-40). The "BI/NAP1/027" strain of *Clostridium difficile* is also characterized by increased toxin A and toxin B production, by the presence of an additional toxin (binary toxin), and increased resistance to fluoroquinolones (McDonald, LC, *et al.*,(2005), N Engl J Med, 353:2433-41; Warny, M. et al., (2005), Lancet 366:1079-84).

[0105] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds (*i.e.*, "full antibody molecules"), as well as multimers thereof (*e.g.* IgM) or antigen-binding fragments thereof. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "V_H") and a heavy chain constant region (comprised of domains C_H1, C_H2 and C_H3). Each light chain is comprised of a light chain variable region ("LCVR or "V_L") and a light chain constant region (C_L). The V_H and V_L 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 V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In certain embodiments of the invention, the FRs of the antibody (or antigen binding fragment thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0106] Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan *et al.* (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos *et al.* 2002 J Mol Biol 320:415-428).

[0107] CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s)

thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

[0108] The fully human anti-toxin A and/or anti-toxin B monoclonal antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, *e.g.*, only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (*i.e.*, a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, *e.g.*, wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[0109] The present invention also includes fully human anti-toxin A and/or anti-toxin B monoclonal antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes anti-toxin A and anti-toxin B antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, *e.g.*, 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

[0110] The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.,* mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences.

[0111] The term "specifically binds," or “binds specifically to”, or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about $1x10^{-6}$ M or less (*e.g.*, a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. As described herein, antibodies have been identified by surface plasmon resonance, *e.g.*, BIACORE™, which bind specifically to either toxin A, or specifically to toxin B from *C. difficile*, while others have been identified that bind specifically to the carboxy terminal receptor binding domain of both toxin A and B. Moreover, multi-specific antibodies that bind to toxin A or toxin B and one or more additional antigens or a bi-specific that binds to two different regions of toxin A or toxin B are nonetheless considered antibodies that “specifically bind”, as used herein.

[0112] The term “high affinity” antibody refers to those mAbs having a binding affinity to toxin A or toxin B, expressed as K_D, of at least 10^{-8} M; preferably 10^{-9} M; more preferably 10^{-10}M, even more preferably 10^{-11} M, even more preferably 10^{-12} M, as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

[0113] By the term “slow off rate”, “Koff” or “kd” is meant an antibody that dissociates from toxin A or toxin B, or both, with a rate constant of 1×10^{-3} s^{-1} or less, preferably 1×10^{-4} s^{-1} or less, as determined by surface plasmon resonance, *e.g.*, BIACORE™.

[0114] The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody

fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to bind to toxin A or toxin B or both.

[0115] The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety ("immunoconjugate"), such as an antibiotic, a second anti-toxin A or B antibody, or a *C. difficile* vaccine, or a toxoid, or any other therapeutic moiety useful for treating a disease or condition caused by *C. difficile*.

[0116] An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies (Abs) having different antigenic specificities (*e.g.,* an isolated antibody that specifically binds toxin A or toxin B, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than toxin A or toxin B.

[0117] A "blocking antibody" or a "neutralizing antibody", as used herein (or an "antibody that neutralizes toxin A and/or toxin B activity"), is intended to refer to an antibody whose binding to toxin A and/or toxin B results in inhibition of at least one biological activity of toxin A and/or toxin B. For example, an antibody of the invention may aid in preventing the primary disease caused by *C. difficile.* Alternatively, an antibody of the invention may demonstrate the ability to prevent a recurrence or relapse of the disease caused by *C. difficile*, or at least one symptom caused by *C. difficile* infection, including diarrhea or psudomembranous colitis. This inhibition of the biological activity of toxin A and/or toxin B can be assessed by measuring one or more indicators of toxin A and/or toxin B biological activity by one or more of several standard *in vitro* assays (such as a neutralization assay, as described herein) or *in vivo* assays known in the art (for example, animal models to look at protection from challenge with *C. difficile* following administration of one or more of the antibodies described herein).

[0118] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

[0119] The term "K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0120] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids,

sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[0121] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0122] As applied to polypeptides, the term "substantial similarity" or “substantially similar” means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, *e.g.*, Pearson (1994) Methods Mol. Biol. 24: 307-331. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443 45. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0123] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative

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

[0124] In specific embodiments, the antibody or antibody fragment for use in the method of the invention may be mono-specific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise an Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 mAbs; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 mAbs; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 mAbs. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

[0125] By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

General Description

[0126] *Clostridium difficile* is a gram-positive, spore-forming, toxin producing bacterium, which

is a leading cause of nosocomial antibiotic-associated diarrhea and colitis in humans (Bartlett, J.G. *et al.* (1978), N. Engl. J. Med. 298:531-534; Kyne, L., *et al.* (2001), Clin. N. Am. 30:753-777). The perturbation of the colonic environment resulting from administration of broad-spectrum antibiotics leads to colonization of the gut by the bacterium (Johnson, S.C. *et al.* (1990), Lancet 336:97-100). A large percentage of this patient population that becomes colonized with *C. difficile* develops diarrhea, which in certain instances leads to pseudomembranous colitis, which is believed to be due to the production of two exotoxins by *C. difficile*, toxin A and toxin B. Treatment consists of the discontinuation of the offending antibiotic, or alterations in the dosing of the offending antibiotic, or no change in the offending antibiotic, followed by the administration of metronidazole, vancomycin, or fidaxomicin. While this treatment regimen is usually successful, many patients relapse when therapy is discontinued (Fekety, R., (1997), Am. J. Gastroenterology, 92:739-750). Furthermore, in many instances, the *C. difficile* bacterium becomes resistant to the therapy used, thus leading to treatment failures and in some instances increased mortality rates (Dworczynski, A. *et al.* (1991), Cytobios. 65:149-153; Fekety, R. *et al.* (1993), JAMA, 269:71-75). Accordingly, there is a need for more effective therapies to combat this disease and/or to prevent the recurrence of this disease in patients colonized with *C. difficile*. In addition, there is a need to treat patients who are at risk for developing a *C. difficile* infection by prophylactic administration of an effective agent. Included in this at risk patient population are the elderly, in particular, patients 65 years of age and older, although patients younger than 65 may be at greater risk depending on the presence of any underlying disease that may predispose them to infection with *C. difficile*. Patients that have been infected with *C. difficile* previously may be at greater risk of recurrences. Other patients at risk include patients who are pre-disposed to a *C. difficile* infection because of an underlying medical condition, or patients who are hospitalized for long periods of time (at least one week or longer) and/or, who are on long term treatment (≥ 14 days) with broad spectrum antibiotics, as well as patients who are on proton pump inhibitors to treat gastroesophageal reflux disease (GERD), stomach and small intestine ulcers and inflammation of the esophagus. These agents include dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, or rabeprazole sodium. Other agents that are under study for placing a patient at risk for developing a *C. difficile* infection include histamine-H2 receptor blockers, such as cimetidine, famotidine, nizatidine and ranitidine. Other studies noted an age-specific incidence of *C. difficile*-associated diarrhea, more specifically, an increase in patients after the age of 50 years, and an increase in mortality rate in patients after the age of 60 (Loo, VG, *et al.*, (2005), N Engl J Med 353:2442—9). This study was in fact, consistent with an earlier study that showed an age-related increase in the incidence of positive assays for *C. difficile* toxin (Karlström, O. *et al.* (1998), Clin Infect Dis 26:141-5).

[0127] To address the need for more effective therapies against *C. difficile*, many studies have been conducted to determine if anti-toxin A and/or B antibodies, when used alone, or as adjunct

therapy, could be used as a means of treating this disease, or at least as a means of preventing the recurrence of the diarrhea or colitis associated with *C. difficile* infection. (Corthier, et al. (1991), Infect. Immun. 59(3):1192-1195; Kink, J.A. and Willilams, J.A., (1998), Infect. Immun. 66(5):2018-2025; Lowy, I. et al. (2010), N. Engl. J. Med. 362(3):197-205; Babcock, G.J., et al.; (2006), Infection and Immunity, 74(11):6339-6347). More particularly, animal models of infection with *C. difficile* have been used to study the effect of antibodies to toxin A and/or toxin B from *C. difficile* on primary infection, as well as on relapse rates *in vivo* (Corthier, G. *et al.* (1991), Infect. Immun. 59(3):1192-1195; Kink, J.A. et al. (1998), Infect. Immun. 66(5):2018-2025; Babcock, G.J. *et al.* (2006), 74(11):6339-6347). The results in animal models of *C. difficile* showed significant protection, thus prompting further clinical trials using anti-toxin A and anti-toxin B antibodies in human patients with the disease (Lowy, I., (2010), N. Engl. J. Med. 362(3):197-205).

[0128] The antibodies described herein demonstrate specific binding to toxin A and/or to toxin B of *C. difficile* and may be useful for treating patients suffering from infection with *C. difficile*. The use of such antibodies may be an effective means of treating patients suffering from a primary infection with *C. difficile*, or they may be used to prevent a relapse of the disease and the accompanying symptoms associated with the disease, or may be used to lessen the severity of the diarrhea or colitis associated with a primary infection or with the recurrence of the infection. They may be used alone or as adjunct therapy with other therapeutic moieties or modalities known in the art for treating *C. difficile* infections, such as, but not limited to, antibiotic therapy, for example, with metronidazole, vancomycin, or fidaxomicin. They may be used in conjunction with a *C. difficile* vaccine, or with use of a toxoid, or with a second or third different antibody specific for toxin A and/or B.

[0129] In certain embodiments of the invention, combinations of the antibodies of the invention may be used to treat an infection caused by a hypervirulent strain of *C. difficile*. The most notable hypervirulent epidemic isolate group to date is one referred to as "BI/NAP1/027". This has been associated with outbreaks of *C. difficile* infections throughout Europe and North America. Isolates that fall into this designation are characterized by increased toxin A and toxin B production, by the presence of an additional toxin (binary toxin) and by an increased resistance to fluoroquinolones (McDonald, LC, *et al.,* (2005), N Engl J Med 353:2433-41; Warny, ME, *et al.,* (2005), Lancet 366:1079-84). This group of isolates may also be referred to as the North American pulsed-field type 1 (NAP1), ribotype 027, group BI strains. This group of strains contains an 18 base pair *tcdC* gene deletion and the binary toxin, which it produces is encoded by *cdtA* and *cdtB* genes. It has been reported that this group produces toxin A and toxin B in quantities 16 and 23 times, respectively, greater than control strains (Warny, ME, *et al.,* (2005), Lancet 366:1079-84). Since the antibodies of the present invention have been shown to neutralize the toxin produced by four different clinically isolated *C. difficile* BI/NAP1/027 strains (VA5, VA17, 6336 and 6443), it is envisioned that compositions comprising

the antibodies of the present invention may be administered therapeutically to patients suffering from an infection with the above-noted hypervirulent strains of *C. difficile*, or may be administered prophylactically to patients who are at risk for developing an infection with the hypervirulent strains noted herein, as well as with any other clinically relevant hypervirulent strains. The means by which to identify these strains are known to those skilled in the art, and these methods may include pulsed-field gel electrophoresis (PFGE) of *C. difficile* isolates (See for example, Fawley, WN, *et al.*, (2002), J. Clin Microbiol 40:3546-7), PCR analyses for binary toxin genes and partial deletions of the *tcdC* gene (See, for example, Gonçalves, C. *et al.* (2004), J Clin Microbiol 42:1933-9; and Cohen, SH et al., (2000), J Infect Dis 181:659-63), and restriction-endonuclease analyses (See, for example, Clabots, CR, *et al.*, (1993), J Clin Microbiol 31:1870-5).

[0130] In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a native, inactivated, toxin A (See GenBank accession number CAA63564 (SEQ ID NO: 378)), or toxin B (See GenBank accession number CAJ67492 (SEQ ID NO: 380)) from *C. difficile*, or with a recombinant, but inactivated form of the toxins, or toxin fragments, followed by immunization with a secondary immunogen, or with an immunogenically active fragment of the native toxin. Animals may be immunized with either inactivated toxin A alone or inactivated toxin B alone, or with both inactivated toxin A and inactivated toxin B concurrently. The toxins can be inactivated prior to use as an immunogen using standard procedures for preparing toxoids, including by treatment with formaldehyde, glutaraldehyde, peroxide, or oxygen treatment (Relyveld, et al. *Methods in Enzymology*, 93:24, 1983, Woodrow and Levine, eds. *New Generation Vaccines*, Marcel Dekker, Inc., New York, 1990). Another means of inactivation is by use of UDP-dialdehyde (Genth et al., (2000), Infect. Immun. 68(3):1094-1101), which may act to preserve the native structure of the toxin compared to other inactivation methods, thereby enhancing the likelihood of eliciting antibodies that are more reactive with the native toxin.

[0131] Alternatively, mutant toxins from *C. difficile*, which exhibit reduced toxicity, may be produced using standard recombinant techniques and used as immunogens (See, for example, US 5,085,862; 5,221,618; 5,244,657; 5,332,583; 5,358,868; and 5,433,945). Such mutants may contain deletions or point mutations in the active site of the toxin.

[0132] The immunogen may be a biologically active and/or immunogenic fragment of native toxin A or toxin B, or DNA encoding the active fragment thereof. The fragment may be derived from the N-terminal or C-terminal domain of either toxin A or toxin B. The fragment may be derived from any of the known domains of toxin A or toxin B (See Figure 1), including the glucosylating enzymatic domain (A), the autocatalytic processing domain (C), the translocating domain (D) or the binding domain (B). In certain embodiments of the invention, the immunogen is the carboxy terminal receptor binding domain of toxin A that ranges from about amino acid residues 1832-2710 of SEQ ID NO: 378. In certain embodiments of the invention, the

immunogen is the carboxy terminal receptor binding domain of toxin A that is shown in SEQ ID NO: 375. In certain embodiments of the invention, the immunogen is the carboxy terminal receptor binding domain of toxin B that ranges from about amino acid residues 1834-2366 of SEQ ID NO: 380. In certain embodiments of the invention, the immunogen is the carboxy terminal receptor binding domain of toxin B that is shown in SEQ ID NO: 376.

[0133] The full-length amino acid sequence of toxin A from *C. difficile* is shown as SEQ ID NO: 378.

[0134] The full-length amino acid sequence of toxin B from *C. difficile* is shown as SEQ ID NO: 380.

[0135] In certain embodiments, antibodies that bind specifically to *C. difficile* toxin A or toxin B may be prepared using fragments of the above-noted regions, or peptides that extend beyond the designated regions by about 5 to about 20 amino acid residues from either, or both, the N or C terminal ends of the regions described herein. In certain embodiments, any combination of the above-noted regions or fragments thereof may be used in the preparation of toxin A or toxin B specific antibodies. In certain embodiments, any one or more of the above-noted regions of toxin A or toxin B, or fragments thereof may be used for preparing monospecific, bispecific, or multispecific antibodies.

Antigen-Binding Fragments of Antibodies

[0136] Unless specifically indicated otherwise, the term "antibody," as used herein, shall be understood to encompass antibody molecules comprising two immunoglobulin heavy chains and two immunoglobulin light chains (*i.e.*, "full antibody molecules") as well as antigen-binding fragments thereof. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to either toxin A and/or toxin B of *C. difficile*. An antibody fragment may include a Fab fragment, a $F(ab')_2$ fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and (optionally) constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino

acids, etc.

[0137] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0138] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H - V_H, V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0139] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H -C_H1; (ii) V_H -C_H2; (iii) V_H -C_H3; (iv) V_H -C_H1-C_H2; (v) V_H -C_H1-C_H2-C_H3; (vi) V_H -C_H2-C_H3; (vii) V_H -C_L; (viii) V_L -C_H1; (ix) V_L -C_H2; (x) V_L -C_H3; (xi) V_L -C_H1-C_H2; (xii) V_L -C_H1-C_H2-C_H3; (xiii) V_L -C_H2-C_H3; and (xiv) V_L -C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[0140] As with full antibody molecules, antigen-binding fragments may be mono-specific or multi-specific (*e.g.*, bi-specific). A multi-specific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is

capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multi-specific antibody format, including the exemplary bi-specific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

Preparation of Human Antibodies

[0141] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to toxin A and/or toxin B of *C. difficile*.

[0142] Using VELOCIMMUNE® technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE®) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to toxin A and/or toxin B of *C. difficile* are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[0143] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[0144] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0145] In general, the antibodies of the instant invention possess very high affinities, typically

possessing K_D of from about 10^{-12} through about 10^{-9} M, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

[0146] The anti-toxin A and anti-toxin B antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind toxin A or toxin B. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antibody or antibody fragment that is essentially bioequivalent to an antibody or antibody fragment of the invention.

[0147] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, *e.g.*, chronic use, and are considered medically insignificant for the particular drug product studied.

[0148] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0149] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0150] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0151] Bioequivalence may be demonstrated by *in vivo* and/or *in vitro* methods.

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

[0152] Bioequivalent variants of the antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, *e.g.*, mutations that eliminate or remove glycosylation.

Biological Characteristics of the Antibodies

[0153] In general, the antibodies of the present invention may function by binding to either toxin A or to toxin B of *C. difficile*, or to both toxin A and toxin B of *C. difficile* (cross-reactive antibodies), or to a fragment of either A or B.

[0154] In certain embodiments, the antibodies of the present invention may bind to an epitope located in at least the C-terminal receptor binding domain of toxin A and/or toxin B of *C. difficile*. In one embodiment, the antibodies may bind to the C-terminal region of toxin A, ranging from amino acid residue 1832-2710 of the carboxy terminal receptor binding domain of toxin A, which spans amino acid residues 1832-2710 of SEQ ID NO: 378. In certain embodiments of the invention, the antibodies may bind the carboxy terminal receptor binding domain of toxin A that is shown in SEQ ID NO: 375. In certain embodiments of the invention, the antibodies may interact with, or bind to, amino acid residues 468-863 of the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, the sequence of which is shown in SEQ ID NO: 375. In certain embodiments of the invention, the antibodies may interact with, or bind to, an epitope in the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, wherein the epitope is selected from the group consisting of residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610 of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 375, residues 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375. In one embodiment, the antibody that binds to or interacts with an epitope in the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, selected from the group consisting of residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610

of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 375, residues 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375 comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 146/154. In one embodiment, the antibody that binds to or interacts with an epitope in the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, selected from the group consisting of residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610 of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 375, residues 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375 is combined with a second antibody that binds specifically to toxin B of *Clostridium difficile* in a pharmaceutical composition. In one embodiment, this second antibody that interacts with or binds to toxin B of *Clostridium difficile* comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282.

[0155] In certain embodiments of the invention, the antibodies may bind to the carboxy terminal receptor binding domain of toxin B that ranges from about amino acid residues 1834-2366 of SEQ ID NO: 380. In certain embodiments of the invention, the antibodies may bind to the carboxy terminal receptor binding domain of toxin B that is shown in SEQ ID NO: 376.

[0156] In certain embodiments, the antibodies of the present invention may function by blocking or inhibiting the toxicity associated with toxin A of *C. difficile* by binding to any other region or fragment of the full length native toxin A protein, the amino acid sequence of which is shown in SEQ ID NO: 378, which is encoded by the nucleic acid sequence shown in SEQ ID NO: 377.

[0157] In certain embodiments, the antibodies of the present invention may function by blocking or inhibiting the toxicity associated with toxin B of *C. difficile* by binding to any other region or fragment of the full length native toxin B protein, the amino acid sequence of which is shown in SEQ ID NO: 380, which is encoded by the nucleic acid sequence shown in SEQ ID NO: 379.

[0158] In certain embodiments, the antibodies of the present invention may be bi-specific antibodies. The bi-specific antibodies of the invention may bind one epitope in toxin A and may also bind one epitope in toxin B. In certain embodiments, the bi-specific antibodies of the invention may bind two different epitopes in toxin A. In certain embodiments, the bi-specific antibodies of the invention may bind two different epitopes in toxin B. In certain embodiments, the bi-specific antibodies of the invention may bind to two different sites within the same domain on either one of toxin A or toxin B, or may bind to the same domain on both toxin A and toxin B.

[0159] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds to the carboxy terminal receptor binding domain of both toxin A and toxin B of *C. difficile*, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 18, 34, 50, 66 and 82, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the

group consisting of SEQ ID NO: 26, 42, 58, 74 and 90, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 24, 40, 56, 72 and 88, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 32, 48, 64, 80 and 96, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 20, 36, 52, 68 and 84, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 22, 38, 54, 70 and 86, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 28, 44, 60, 76 and 92, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 30, 46, 62, 78 and 94, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds to toxin A and toxin B with a K_D equal to or less than 10^{-9}M.

[0160] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to toxin A (but not to toxin B) of *C. difficile*, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 98,114,130,146 and 162, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 106, 122, 138, 154 and 170, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 104,120,136,152 and 168, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 112, 128, 144, 160 and 176, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 100, 116, 132, 148 and 164, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence

selected from the group consisting of SEQ ID NO: 6, 102, 118, 134, 150 and 166, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 108, 124, 140, 156 and 172, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 110, 126, 142, 158 and 174, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) demonstrates a K_D equal to or less than 10^{-9}M; (vi) demonstrates neutralization of Toxin A (at a concentration of 32pM) with an IC50 ranging from about 7pM to about 65pM in a cell viability assay.

[0161] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to toxin B (but not to toxin A) of *C. difficile*, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO:186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO:184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344 and 360, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO:192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352 and 368, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 180,196, 212, 228, 244, 260, 276, 292, 308, 324, 340 and 356, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342 and 358, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348 and 364, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 190, 206, 222, 238, 254, 270, 286, 302, 318,

334, 350 and 366, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) demonstrates a K_D equal to or less than 10^{-9}M; (vi) demonstrates neutralization of Toxin B (at a concentration of 0.03pM) with an IC50 ranging from about 25pM to about 320pM in a cell viability assay.

[0162] Certain anti-toxin A or anti-toxin B antibodies of the present invention are able to bind to and neutralize the toxicity of either toxin A, or toxin B, or both, of *C. difficile*, as determined by *in vitro* or *in vivo* assays. The ability of the antibodies of the invention to bind to and neutralize the activity of the toxins may be measured using any standard method known to those skilled in the art, including binding assays, or neutralization of toxicity (protection from cell death) assays, as described herein.

[0163] Non-limiting, exemplary *in vitro* assays for measuring binding activity are illustrated in Examples 4, 5 and 6, herein. In Examples 4 and 5, the binding affinities and kinetic constants of human anti-toxin A or anti-toxin B antibodies were determined by surface plasmon resonance and the measurements were conducted on a T200 Biacore instrument. In Example 6, the binding studies were conducted using size exclusion chromatography. In Example 7, a neutralization bioassay was developed in Vero cells to detect cell viability after treatment with toxin A or B and antibodies to either toxin A or to toxin B.

[0164] The present invention also includes anti-toxin A or B antibodies and antigen binding fragments thereof which bind to at least one biologically active fragment of any of the following proteins, or peptides: SEQ ID NO: 378 (full length toxin A), residue numbers 1832-2710 of SEQ ID NO: 378 (C-terminal domain of toxin A); SEQ ID NO: 380 (full length toxin B), residues 1834-2366 of SEQ ID NO: 380; SEQ ID NO: 375 (carboxy terminal receptor binding domain of toxin A); or SEQ ID NO: 376. The present invention also provides for antibodies that interact with or bind to an epitope within the carboxy terminal receptor binding domain of toxin A produced by *Clostridium difficile*, or an antigen binding fragment thereof, wherein the epitope is contained within residues ranging from about residue 468 to about 863 of SEQ ID NO: 375. In one embodiment, the epitope for an antibody that binds toxin A is selected from the group consisting of residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610 of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 375, residues 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375. Any of the toxin A or toxin B peptides described herein, or fragments thereof, may be used to generate anti-toxin A or anti-toxin B antibodies.

[0165] The peptides may be modified to include addition or substitution of certain residues for tagging or for purposes of conjugation to carrier molecules, such as, KLH. For example, a cysteine may be added at either the N terminal or C terminal end of a peptide, or a linker sequence may be added to prepare the peptide for conjugation to, for example, KLH for immunization. The antibodies specific for toxin A or toxin B may contain no additional labels or moieties, or they may contain an N-terminal or C-terminal label or moiety. In one embodiment,

the label or moiety is biotin. In a binding assay, the location of a label (if any) may determine the orientation of the peptide relative to the surface upon which the peptide is bound. For example, if a surface is coated with avidin, a peptide containing an N-terminal biotin will be oriented such that the C-terminal portion of the peptide will be distal to the surface.

Epitope Mapping and Related Technologies

[0166] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques include, for example, a routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY) can be performed. Other methods include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol Biol 248:443-63), peptide cleavage analysis crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of the interface. As a result, amino acids that form part of the protein/antibody interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues that correspond to the specific amino acids with which the antibody interacts. *See, e.g.*, Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem. 73*:256A-265A.

[0167] The term "epitope" refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0168] Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (US 2004/0101920). Each

category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce mAbs having the desired characteristics. MAP may be used to sort the antibodies of the invention into groups of antibodies binding different epitopes.

[0169] In certain embodiments, the anti-toxin A or anti-toxin B antibody or antigen-binding fragments thereof binds an epitope within any one of the regions exemplified in Figure 1, or in SEQ ID NOS: 378, or 380, or at least one of the carboxy terminal receptor binding domains of toxin A or toxin B, or to a fragment thereof, wherein the carboxy terminal receptor binding domain of toxin A is shown in SEQ ID NO: 375, and wherein the carboxy terminal receptor binding domain of toxin B is shown as SEQ ID NO: 376.

[0170] The present invention includes anti-toxin A or anti-toxin B antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein in Table 1. Likewise, the present invention also includes anti-toxin A or anti-toxin B antibodies that compete for binding to toxin A or B or a toxin A or B fragment with any of the specific exemplary antibodies described herein in Table 1.

[0171] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-toxin A or anti-toxin B antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-toxin A or anti-toxin B antibody of the invention, the reference antibody is allowed to bind to a toxin A or B protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the toxin A or B molecule is assessed. If the test antibody is able to bind to toxin A or B following saturation binding with the reference anti-toxin A or anti-toxin B antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-toxin A or anti-toxin B antibody. On the other hand, if the test antibody is not able to bind to the toxin A or B molecule following saturation binding with the reference anti-toxin A or anti-toxin B antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-toxin A or anti-toxin B antibody of the invention.

[0172] To determine if an antibody competes for binding with a reference anti-toxin A or anti-toxin B antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a toxin A or B molecule under saturating conditions followed by assessment of binding of the test antibody to the toxin A or B molecule. In a second orientation, the test antibody is allowed to bind to a toxin A or B molecule under saturating conditions followed by assessment of binding of the reference antibody to the toxin A or B molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the toxin A or B molecule, then it is concluded that the test antibody and the reference antibody compete for binding to toxin A or B. As will be appreciated by a person

of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the identical epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

[0173] Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, *e.g.,* Junghans *et al.*, Cancer Res. 1990 50:1495-1502). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0174] Additional routine experimentation (*e.g.*, peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

Immunoconjugates

[0175] The invention encompasses a human anti-toxin A or anti-toxin B monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an agent that is capable of reducing the severity of primary infection with *C. difficile*, or to ameliorate at least one symptom associated with *C. difficile* infection, including diarrhea or colitis, or the severity thereof. Such an agent may be a second different antibody to either or both toxin A or toxin B of *C. difficile*, or a toxoid, or a *C. difficile* vaccine. The type of therapeutic moiety that may be conjugated to the anti-toxin A or anti-toxin B antibody and will take into account the condition to be treated and the desired therapeutic effect to be achieved. Alternatively, if the desired therapeutic effect is to treat the sequelae or symptoms associated with *C. difficile* infection, or any other condition resulting from such infection, such as, but not limited to, pseudomembranous colitis, it may be advantageous to conjugate an agent appropriate to treat the sequelae or symptoms of the condition, or to alleviate any side effects of the antibodies of the invention. Examples of suitable agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Multi-specific Antibodies

[0176] The antibodies of the present invention may be mono-specific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target

polypeptide. See, *e.g.,* Tutt *et al.,* 1991, J. Immunol. 147:60-69; Kufer *et al*., 2004, Trends Biotechnol. 22:238-244. The antibodies of the present invention can be linked to or co-expressed with another functional molecule, *e.g.*, another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (*e.g.,* by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multi-specific antibody with a second binding specificity. For example, the present invention includes bi-specific antibodies wherein one arm of an immunoglobulin is specific for toxin A of *C. difficile*, or a fragment thereof, and the other arm of the immunoglobulin is specific for toxin B of *C. difficile*, or a second therapeutic target, or is conjugated to a therapeutic moiety. In certain embodiments of the invention, one arm of an immunoglobulin is specific for an epitope on the C-terminal domain of toxin A or a fragment thereof, and the other arm of the immunoglobulin is specific for an epitope on the C-terminal domain of toxin B, or a fragment thereof.

[0177] An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_{H3} domain and a second Ig C_{H3} domain, wherein the first and second Ig C_{H3} domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_{H3} domain binds Protein A and the second Ig C_{H3} domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_{H3} may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_{H3} include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

Therapeutic Administration and Formulations

[0178] The invention provides therapeutic compositions comprising the anti-toxin A or anti-toxin B antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing

vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell *et al.* "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0179] The dose of each of the antibodies of the invention may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibodies of the present invention are used for treating a *C. difficile* infection in a patient, or for treating one or more symptoms associated with a *C. difficile* infection, such as the diarrhea or colitis associated with a *C. difficile* infection in a patient, or for preventing a relapse of the disease, or for lessening the severity of the disease, it is advantageous to administer each of the antibodies of the present invention intravenously or subcutaneously normally at a single dose of about 0.01 to about 30 mg/kg body weight, more preferably about 0.1 to about 20 mg/kg body weight, or about 0.1 to about 15 mg/kg body weight, or about 0.02 to about 7 mg/kg body weight, or about 0.03 to about 5 mg/kg body weight, or about 0.05 to about 3 mg/kg body weight, or about 1 mg/kg body weight, or about 3.0 mg/kg body weight, or about 10 mg/kg body weight, or about 20 mg/kg body weight. Multiple doses may be administered as necessary. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. In certain embodiments, the antibodies or antigen-binding fragments thereof of the invention can be administered as an initial dose of at least about 0.1 mg to about 800 mg, about 1 to about 600 mg, about 5 to about 300 mg, or about 10 to about 150 mg, to about 100 mg, or to about 50 mg. In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of the antibodies or antigen-binding fragments thereof in an amount that can be approximately the same or less than that of the initial dose, wherein the subsequent doses are separated by at least 1 day to 3 days; at least one week, at least 2 weeks; at least 3 weeks; at least 4 weeks; at least 5 weeks; at least 6 weeks; at least 7 weeks; at least 8 weeks; at least 9 weeks; at least 10 weeks; at least 12 weeks; or at least 14 weeks.

[0180] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, *e.g.,* encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, *e.g.*, Wu *et al.* (1987) J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, transdermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.,* oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0181] The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see, for example, Langer (1990) Science 249:1527-1533).

[0182] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose.

[0183] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (*e.g.*, ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, *e.g.*, sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0184] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0185] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ),

OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK ™ Autoinjector (Amgen, Thousands Oaks, CA), the PENLET ™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.) and the HUMIRA ™ Pen (Abbott Labs, Abbott Park, IL), to name only a few.

[0186] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Administration Regimens

[0187] According to certain embodiments of the present invention, multiple doses of an antibody to toxin A and/or B of *Clostridium difficile* may be administered to a subject over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a subject multiple doses of an antibody to toxin A and/or B. As used herein, "sequentially administering" means that each dose of antibody to toxin A and/or B is administered to the subject at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an antibody to toxin A and/or B, followed by one or more secondary doses of the antibody to toxin A and/or B, and optionally followed by one or more tertiary doses of the antibody to toxin A and/or B.

[0188] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the antibody to toxin A and/or B. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of antibody to toxin A and/or B, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of antibody to toxin A and/or B contained in the initial, secondary and/or tertiary doses vary from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (*e.g.*, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses"

followed by subsequent doses that are administered on a less frequent basis (*e.g.*, "maintenance doses").

[0189] In one exemplary embodiment of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (*e.g.*, 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of antibody to toxin A and/or B which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0190] The methods according to this aspect of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of an antibody to toxin A and/or B. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0191] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

Therapeutic Uses of the Antibodies

[0192] Due to their interaction with toxin A and/or toxin B of *C. difficile,* the present antibodies are useful for treating the primary *C. difficile* disease or condition, or at least one symptom associated with the disease or condition, such as diarrhea or colitis, or for preventing a relapse of the disease, or for lessening the severity, duration, and/or frequency of recurrences of the disease. The antibodies of the invention are also contemplated for prophylactic use in patients at risk for developing or acquiring a *C. difficile* infection. These patients include the elderly (for example, in anyone 65 years of age or older), or patients immunocompromised due to illness or treatment with immunosuppressive therapeutics, or patients who may have an underlying medical condition that predisposes them to a *C. difficile* infection (for example, cancer,

inflammatory bowel disease, pre-liver transplant patients with ascites accumulation), or patients that are hospitalized for long periods of time (for example, in some cases this time period may vary from as little as two or three days, but generally can be from one week, to two weeks or longer), making them prone to acquiring nosocomial infections, or patients on long term treatment (≥ 14 days) with broad spectrum antibiotics (in some instances, patients may acquire the infection within 24 hours if the gut is disregulated, but in other instances this may take much longer, for example, one week or longer), or patients on therapy with proton pump inhibitors for treatment of gastrointestinal disorders. It is contemplated that the antibodies of the invention may be used alone, or in conjunction with a second agent, or third agent for treating the *C. difficile* infection, or for alleviating at least one symptom or complication associated with the *C. difficile* infection, such as the diarrhea or colitis associated with, or resulting from such an infection. The second or third agents may be delivered concurrently with the antibodies of the invention, or they may be administered separately, either before or after the antibodies of the invention.

[0193] In yet a further embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for treating patients suffering from a *C. difficile* infection, including those infections caused by a clinically relevant hypervirulent strain of *Clostridium difficile*, or the diarrhea and colitis associated with a *C. difficile* infection. In yet another embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for reducing the severity of a primary infection with *C. difficile*, or for reducing the severity, duration of, and/or number of recurrences with *C. difficile*. In a further embodiment of the invention the present antibodies are used as adjunct therapy with any other agent useful for treating *C. difficile* infections, including probiotics, antibiotics, toxoids, vaccines, or any other palliative therapy known to those skilled in the art.

Combination Therapies

[0194] The methods of the present invention, according to certain embodiments, comprise administering to the subject one or more additional therapeutic agents in combination with an antibody to toxin A and/or toxin B of *Clostridium difficile*. As used herein, the expression "in combination with" means that the additional therapeutic agents are administered before, after, or concurrent with the pharmaceutical composition comprising the anti-toxin A and/or B antibodies. The term “in combination with” also includes sequential or concomitant administration of the anti-toxin A and/or B antibodies and a second therapeutic agent.

[0195] For example, when administered "before" the pharmaceutical composition comprising the anti-toxin A and/or B antibodies, the additional therapeutic agent may be administered about 72 hours, about 60 hours, about 48 hours, about 36 hours, about 24 hours, about 12 hours, about 10 hours, about 8 hours, about 6 hours, about 4 hours, about 2 hours, about 1 hour, about 30 minutes, about 15 minutes or about 10 minutes prior to the administration of the

pharmaceutical composition comprising the anti-toxin A and/or B antibodies. When administered "after" the pharmaceutical composition comprising the anti-toxin A and/or B antibodies, the additional therapeutic agent may be administered about 10 minutes, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours or about 72 hours after the administration of the pharmaceutical composition comprising the anti-toxin A and/or B antibodies. Administration "concurrent" or with the pharmaceutical composition comprising the anti-toxin A and/or B antibodies means that the additional therapeutic agent is administered to the subject in a separate dosage form within less than 5 minutes (before, after, or at the same time) of administration of the pharmaceutical composition comprising the anti-toxin A and/or B antibodies, or administered to the subject as a single combined dosage formulation comprising both the additional therapeutic agent and the anti-toxin A and/or B antibodies.

[0196] Combination therapies may include an anti-toxin A or anti-toxin B antibody of the invention and any additional therapeutic agent that may be advantageously combined with an antibody of the invention, or with a biologically active fragment of an antibody of the invention.

[0197] For example, a second or third therapeutic agent may be employed to aid in reducing the bacterial load in the gut, such as an antibiotic that is bacteriostatic or bacteriocidal with respect to *C. difficile*. Exemplary antibiotics include vancomycin, metronidazole, or fidaxomicin. The antibodies may also be used in conjunction with other therapies, such as toxoids, vaccines specific for *C. difficile,* or probiotic agents, such as *Saccharomyces boulardii*.

Diagnostic Uses of the Antibodies

[0198] The anti-toxin A or anti-toxin B antibodies of the present invention may also be used to detect and/or measure toxin A or B in a sample, *e.g.*, for diagnostic purposes. It is envisioned that confirmation of an infection thought to be caused by *C. difficile* may be made by measuring the presence of either toxin A or toxin B through use of any one or more of the antibodies of the invention. Exemplary diagnostic assays for toxin A or toxin B may comprise, *e.g.*, contacting a sample, obtained from a patient, with an anti-toxin A or anti-toxin B antibody of the invention, wherein the anti-toxin A or anti-toxin B antibody is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate toxin A or toxin B protein from patient samples. Alternatively, an unlabeled anti-toxin A or anti-toxin B antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure toxin A or toxin B in a sample include enzyme-linked immunosorbent assay (ELISA),

radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0199] Samples that can be used in *C. difficile* diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of either *C. difficile* toxin A or toxin B protein, or fragments thereof, under normal or pathological conditions. Generally, levels of toxin A or toxin B in a particular sample obtained from a healthy patient (*e.g.*, a patient not afflicted with a disease or condition associated with the presence of *C. difficile*) will be measured to initially establish a baseline, or standard, level of toxin A or toxin B from *C. difficile*. This baseline level of toxin A or toxin B can then be compared against the levels of toxin A or toxin B measured in samples obtained from individuals suspected of having a *C. difficile* related disease or condition, or symptoms associated with such disease or condition.

EXAMPLES

[0200] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Generation of Human Antibodies to *Clostridium difficile* toxin A and/or toxin B

[0201] An immunogen comprising any one of the following can be used to generate antibodies to *C. difficile* toxin A and/or toxin B. In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a full length, native, inactivated, toxin A (See GenBank accession number CAA63564 (SEQ ID NO: 378)), and/or toxin B (See GenBank accession number CAJ67492 (SEQ ID NO: 380)) from *C. difficile*, or with a recombinant, but inactivated form of the toxins, or toxin fragments, or a toxoid, followed by immunization with a secondary immunogen, or with an immunogenically active fragment of the native toxin. Animals may be immunized with either inactivated toxin A alone or inactivated toxin B alone, or with both inactivated toxin A and inactivated toxin B, concurrently. The toxins can be inactivated prior to use as an immunogen using standard procedures for preparing toxoids, including by treatment with formaldehyde, glutaraldehyde, peroxide, or oxygen treatment (Relyveld, et al. *Methods in Enzymology*, 93:24, 1983, Woodrow and Levine, eds. *New Generation Vaccines*, Marcel Dekker, Inc., New York, 1990). Another means of inactivation is by use of UDP-dialdehyde (Genth et al., (2000), Infect. Immun. 68(3):1094-1101), which may act to preserve the native structure of the toxin compared to other inactivation

methods, thereby enhancing the likelihood of eliciting antibodies that are more reactive with the native toxin. Alternatively, mutant toxins from *C. difficile*, which exhibit reduced toxicity, may be produced using standard recombinant techniques and used as immunogens (See, for example, US 5,085,862; 5,221,618; 5,244,657; 5,332,583; 5,358,868; and 5,433,945). Such mutants may contain deletions or point mutations in the active site of the toxin.

[0202] In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a biologically active and/or immunogenic fragment of native toxin A or toxin B, or DNA encoding the active fragment thereof. In certain embodiments, the immunogen may be a peptide from the N terminal or C terminal end of toxin A and/or toxin B, or a fragment derived from the N or C terminal peptide of toxin A and/or toxin B. In certain embodiments of the invention, the immunogen is the carboxy terminal receptor binding domain of toxin A that ranges from about amino acid residues 1832-2710 of SEQ ID NO: 378. In certain embodiments of the invention, the immunogen is the carboxy terminal receptor binding domain of toxin A that is shown in SEQ ID NO: 375. In certain embodiments of the invention, the immunogen is the carboxy terminal receptor binding domain of toxin B that ranges from about amino acid residues 1834-2366 of SEQ ID NO: 380. In certain embodiments of the invention, the immunogen is the carboxy terminal receptor binding domain of toxin B that is shown in SEQ ID NO: 376.

[0203] Accordingly, in one embodiment, the antibodies of the invention were obtained from mice immunized with either an inactivated full length toxin A (toxoid), or an inactivated full length toxin B (toxoid), or both toxoids. Furthermore, in one embodiment, antibodies were obtained from mice immunized with a polypeptide comprising amino acid sequences from the carboxy-terminal receptor binding domain of *C. difficile* toxin A, or with a polypeptide comprising amino acid sequences from the carboxy-terminal receptor binding domain of *C. difficile* toxin B, or both, concurrently.

[0204] In certain embodiments, antibodies that bind specifically to *C. difficile* toxin A or toxin B may be prepared using fragments of the above-noted regions, or peptides that extend beyond the designated regions by about 5 to about 20 amino acid residues from either, or both, the N or C terminal ends of the regions described herein. In certain embodiments, any combination of the above-noted regions or fragments thereof may be used in the preparation of toxin A or toxin B specific antibodies. In certain embodiments, any one or more of the above-noted regions of toxin A or toxin B, or fragments thereof may be used for preparing monospecific, bispecific, or multispecific antibodies.

[0205] The full length proteins, or carboxy-terminal fragments thereof, that were used as immunogens, as noted above, were administered directly, with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse comprising DNA encoding human Immunoglobulin heavy and kappa light chain variable regions. The antibody immune response was monitored by a *C. difficile* toxin A and/or toxin B-specific immunoassay. When a desired

immune response was achieved splenocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce *C. difficile* toxin A and/or toxin B-specific antibodies. Using this technique, and the various immunogens described above, several anti-*C. difficile* toxin A and toxin B, as well as cross-reactive, chimeric antibodies (*i.e.*, antibodies possessing human variable domains and mouse constant domains) were obtained; certain exemplary antibodies generated in this manner were designated as H1H3067N, H1H3134N, H1H3117N, H1M3123N, H1M3121N and H1M3124N.

[0206] Anti-*C. difficile* toxin A and toxin B antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. 2007/0280945A1. Using this method, several fully human anti-C. difficile toxin A and toxin B antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1H3328P, H1H3324P, H1H3325P, H1H3330P, H1H3350P, H1H3347P, H1H3335P, H1H3344P. H1H3339P, H1H3337P, H1H3343P, H1H3411P, H1H3354P, H1H3317P, H1H3355P, H1H3394P and H1H3401P.

[0207] The biological properties of the exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

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

[0208] Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected antibodies specific for toxin A and/or toxin B from *C. difficile* and their corresponding antibody identifiers. Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (e.g. “H4H”, “H1M, “H2M”), followed by a numerical identifier (e.g. “3117” as shown in Table 1), followed by a “P” or “N” suffix. Thus, according to this nomenclature, an antibody may be referred to as, e.g. “H1H3117”. The H4H, H1M, and H2M prefixes on the antibody designations used herein indicate the particular Fc region of the antibody. For example, an “H2M” antibody has a mouse IgG2 Fc, whereas an “H4H” antibody has a human IgG4 Fc. As will be appreciated by a person of ordinary skill in the art, an H1M or H2M antibody can be converted to an H4H antibody, and vice versa, but in any event, the variable domains (including the CDRs), which are indicated by the numerical identifiers shown in Table 1, will remain the same. Antibodies having the same numerical antibody designation, but differing by a letter suffix of N, B or P refer to antibodies having heavy and light chains with identical CDR sequences but with sequence variations in regions that fall outside of the CDR sequences (*i.e.,* in the framework regions). Thus, N, B and P variants of a particular antibody have identical CDR sequences within their heavy and light chain variable regions but differ from one another within their framework regions.

Antibody Comparators

[0209] Anti-toxin A and anti-toxin B controls were included in the following Examples for comparative purposes. Isotype matched negative controls were also used in the Examples. One anti-toxin A control antibody is designated herein as Control I and is an anti-toxin A antibody with heavy and light chain variable domain sequences of the "3D8" antibody as set forth in US7625559 and US2005/0287150. One anti-toxin B antibody is designated herein as Control II and is an anti-toxin B antibody with heavy and light chain variable domain sequences of the "124-152" antibody as set forth in US7625559 and US2005/0287150. Another anti-toxin A antibody is designated herein as Control III and is an anti-toxin A antibody with heavy and light chain variable domain sequences of the "3358" antibody as set forth in US2009/0087478.

Table 1

	SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
H1H3117N	2	4	6	8	10	12	14	16
H1H3134N	18	20	22	24	26	28	30	32
H1H3067N	34	36	38	40	42	44	46	48
H1H3121N	50	52	54	56	58	60	62	64
H1H3123N	66	68	70	72	74	76	78	80
H1H3124N	82	84	86	88	90	92	94	96
H1H3324P	98	100	102	104	106	108	110	112
H1H3325P	114	116	118	120	122	124	126	128
H1H3328P	130	132	134	136	138	140	142	144
H1H3330P	146	148	150	152	154	156	158	160
H1H3350P	162	164	166	168	170	172	174	176
H1H3317P	178	180	182	184	186	188	190	192
H1H3335P	194	196	198	200	202	204	206	208
H1H3337P	210	212	214	216	218	220	222	224
H1H3339P	226	228	230	232	234	236	238	240
H1H3343P	242	244	246	248	250	252	254	256
H1H3344P	258	260	262	264	266	268	270	272
H1H3347P	274	276	278	280	282	284	286	288
H1H3354P	290	292	294	296	298	300	302	304
H1H3355P	306	308	310	312	314	316	318	320
H1H3394P	322	324	326	328	330	332	334	336
H1H3401P	338	340	342	344	346	348	350	352
H1H3411P	354	356	358	360	362	364	366	368

Example 3. Variable Gene Utilization Analysis

[0210] To analyze the structure of antibodies produced, the nucleic acids encoding antibody variable regions were cloned and sequenced. From the nucleic acid sequence and predicted amino acid sequence of the antibodies, gene usage was identified for each Heavy Chain Variable Region (HCVR) and Light Chain Variable Region (LCVR). Table 2 sets forth the gene usage for selected antibodies in accordance with the invention.

Table 2

Antibody	Antibody Identifier	HCVR			LCVR	
	HCVR/LCVR	V_H	D_H	J_H	V_K	J_K
H1H3067N	34/42	3-30	6-6	4	4-1	4
H1H3134N	18/26	3-33	3-10	4	4-1	3
H1H3117N	2/10	3-23	1-7	4	3-20	2
H1H3123N	66/74	3-48	4-11	6	1-5	1
H1H3121N	50/58	3-48	5-18	6	1-5	1
H1H3124N	82/90	3-48	3-22	6	1-5	1
H1H3328P	130/138	3-13	3-10	6	1-27	3
H1H3324P	98/106	3-13	3-10	6	1-27	3
H1H3325P	114/122	3-23	3-10	6	1-5	1
H1H3330P	146/154	3-33	1-7	4	1-39	5
H1H3350P	162/170	3-11	7-27	4	3-15	2
H1H3347P	274/282	3-23	1-26	4	1-16	3
H1H3335P	194/202	3-23	1-26	4	1-16	3
H1H3344P	258/266	3-23	2-15	4	1-16	3
H1H3339P	226/234	3-23	1-26	4	1-16	3
H1H3337P	210/218	3-23	1-26	5	1-16	3
H1H3343P	242/250	3-23	1-26	4	1-16	3
H1H3411P	354/362	3-23	1-1	6	1D-12	2
H1H3354P	290/298	6-1	2-8	4	3-11	2
H1H3317P	178/186	3-30	3-10	4	1D-12	4
H1H3355P	306/314	3-9	1-26	6	1-6	3
H1H3394P	322/330	1-2	2-2	4	3-20	4
H1H3401P	338/346	3-30	1-1	4	1D-12	2

Example 4. Antibody Binding to Toxin A and/or Toxin B from *C. difficile* as Determined by Surface Plasmon Resonance

[0211] Binding affinities and kinetic constants of human monoclonal anti-*Clostridium difficile* toxin A and/or B antibodies were determined by surface plasmon resonance at 37°C (Tables 3-5). Measurements were conducted on a T200 Biacore instrument.

[0212] Antibodies, expressed as human IgG1 Fc (AbPID prefix H1H) or hybridoma (AbPID prefix HxM), were captured onto an anti-human or anti-mouse-Fc sensor surface, respectively

(Mab capture format). Soluble full-length toxin A or B (TechLab), ranging from 5 to 10 nM, was injected over the antibody-captured surface. Antibody-antigen association was monitored for 150 seconds while dissociation in buffer was monitored for 480 seconds. Kinetic analysis was performed to calculate K_D and half-life of antigen/antibody complex dissociation using Biacore T200 evaluation software 1.0.

[0213] As seen in Tables 3-5, three types of antibodies were isolated: antibodies that bound both toxin A and toxin B ("dual binders", see Table 3), antibodies that bound only toxin A (Table 4), and antibodies that bound only toxin B (Table 5). Several antibodies were identified that bound both toxin A and toxin B, including those designated as H2M3121N, H2M3123N, H2M3124N, H1H3067N and H1H3134N and thus were classified as dual binders. Isolated anti-toxin A antibodies bound toxin in the sub-nanomolar (nM) range similar to the isotype matched comparator Mab (control I; see US patent US7625559 for comparator sequences for clone 3D8 (A toxin Ab) and clone 124-152 (B toxin Ab)), while only a few anti-toxin B binders showed affinities in the range of control II isotype matched comparator Mab (clone 124-152) (~200-300pM). Binding dissociation equilibrium constants and dissociative half-lives were calculated from the kinetic rate constants as: $K_D = k_d / k_a$; $T_{1/2}$ (min) = $(\ln 2/k_d)/60$

Table 3: Biacore affinities of anti-*C. difficile* Dual Binding mAbs at 37°C

Binding at 37ºC / Mab Capture Format					
AbPID	**Analyte (Toxin)**	**ka (Ms^{-1})**	**kd (s^{-1})**	**K_D (Molar)**	**T½ (min)**
H2M3121N	Toxin A	9.69E+05	1.66E-04	1.72E-10	69
	Toxin B	6.11E+04	7.58E-05	1.24E-09	152
H2M3123N	Toxin A	1.23E+06	5.93E-04	4.81E-10	19
	Toxin B	3.97E+04	6.54E-05	1.65E-09	176
H2M3124N	Toxin A	1.14E+06	1.98E-04	1.74E-10	58
	Toxin B	3.31E+05	1.00E-06	3.02E-12	11550
H1H3067N	Toxin A	1.44E+05	3.45E-05	2.40E-10	335
	Toxin B	2.54E+03	6.43E-04	2.53E-07	18
H1H3134N	Toxin A	1.02E+05	2.82E-06	2.78E-11	4096
	Toxin B	2.99E+03	9.73E-04	3.25E-07	12

Table 4: Biacore affinities of anti-*C. difficile* Toxin A mAbs at 37°C

Binding at 37ºC / Mab Capture Format					
AbPID	**Analyte**	**ka (Ms^{-1})**	**kd (s^{-1})**	**K_D (Molar)**	**T½ (min)**
H1H3117N	Toxin A	4.38E+05	3.84E-05	7.93E-11	332
H1H3324P	Toxin A	2.51E+05	3.50E-06	1.39E-11	3297
H1H3325P	Toxin A	5.27E+05	5.51E-05	1.05E-10	209
H1H3328P	Toxin A	3.82E+05	3.66E-05	9.57E-11	316
H1H3330P	Toxin A	2.50E+05	1.37E-04	5.47E-10	85
H1H3350P	Toxin A	4.02E+05	4.05E-06	1.01E-11	2854
Control I	Toxin A	3.77E+05	3.24E-05	8.59E-11	58

Table 5: Biacore affinities of anti-*C. difficile* Toxin B mAbs at 37°C

AbPID	Analyte	ka (Ms^{-1})	kd (s^{-1})	K_D (Molar)	T½ (min)
H1H3317P	Toxin B	6.50E+05	7.78E-05	1.20E-10	149
H1H3335P	Toxin B	1.77E+05	4.14E-04	2.34E-09	28
H1H3337P	Toxin B	2.41E+05	9.45E-04	3.93E-09	12
H1H3339P	Toxin B	2.76E+05	5.37E-04	1.95E-09	22
H1H3343P	Toxin B	2.84E+05	4.48E-04	1.58E-09	26
H1H3344P	Toxin B	2.04E+05	8.65E-04	4.24E-09	13
H1H3347P	Toxin B	3.39E+05	8.13E-04	2.40E-09	14
H1H3354P	Toxin B	NB	NB	NB	
H1H3355P	Toxin B	NB	NB	NB	
H1H3394P	Toxin B	4.86E+05	1.62E-04	3.33E-10	72
H1H3401P	Toxin B	4.20E+05	2.41E-04	5.74E-10	48
H1H3411P	Toxin B	2.35E+05	1.59E-04	6.77E-10	73
Control II	Toxin B	2.11E+06	4.59E-04	2.18E-10	25

NB = no binding under the conditions tested

Example 5. Determination of the binding domain for anti-*Clostridium difficile* toxin A and B antibodies using Surface Plasmon Resonance

[0214] Studies were done to determine if anti-*Clostridium difficile* toxin A and/or B antibodies bound to the C-term receptor-Binding Domain (CBD) of each toxin. In these studies, two experimental Biacore formats were employed. The first utilized captured anti-*C. difficile* antibody surfaces in which 100nM of CBD-toxin A-Fc (SEQ ID NO:375) or CBD-toxin B-Fc (SEQ ID NO:376) was flowed over and the responses (RU) recorded. The CBD-toxin reagents were formatted in both human and mouse Fc to enable both hybridoma and human Fc formatted antibody analysis. The second format employed antigen (CBD-Fc) captured surfaces in which 500nM of anti-*C. difficile* mAb was flowed over. In this format, hybridoma or human Fc formatted antibodies were flowed over human and mouse Fc captured antigens, respectively. In both formats a response that was significantly above background (>50 RU) was considered binding to the CBD of toxin A or B (see Table 6). For both anti-toxin A and anti-toxin B antibodies, epitopes that were within and outside the CBD were obtained. Both control I (3D8 antibody from US7625559 and US 2005/0287150) and control II (124-152 antibody from US7625559 and US 2005/0287150) were mapped to the CBD of their respective toxins in agreement with previous reports (data not shown; see US 2005/0287150 and US7625559).

Table 6: Determination of the domain of binding for *C. difficile* antibodies

	C-term Toxin A Binding		C-term Toxin B Binding		
mAb	mAb Capture 100nM CBD-A Binding (RU)	CBD-A Capture 500nM mAB Binding (RU)	mAB Capture 100nM CBD-B Binding (RU)	CBD- B Capture 500nM mAb Binding (RU)	Domain Binding[#]

H2aM3067	-2	237	25	369	C-Term
H1M3117	-3	350	-1	21	C-Term A
H2aM3121	0	23	2	10	Non CBD
H2aM3123	1	23	1	14	Non CBD
H2aM3124	0	29	0	19	Non CBD
H1M3134	-1	195	23	394	C-Term
H1H3324P	269	224	19	-8	C-Term A
H1H3325P	17	3	7	-8	Non CBD
H1H3328P	354	227	35	-6	C-Term A
H1H3330P	441	515	40	-4	C-Term A
H1H3335P	13	5	13	-6	Non CBD
H1H3337P	-17	8	-24	-2	Non CBD
H1H3339P	19	2	14	-2	Non CBD
H1H3343P	11	3	9	-4	Non CBD
H1H3344P	5	5	4	-2	Non CBD
H1H3347P	42	-13	44	7	Non CBD
H1H3354P	-19	-2	-24	-4	Non CBD

Non CBD indicates no binding to C-term receptor Binding Domain of Toxin-A or -B.

Example 6. Determination of the domain of binding for anti-*Clostridium difficile* toxin A and B antibodies using Size Exclusion Chromatography

[0215] As a complimentary method for determining if anti-*Clostridium difficile* toxin A and/or B antibodies bound the C-term receptor Binding Domain (CBD), size exclusion chromatography (SEC) was utilized. Briefly, the CBD of toxin A (SEQ ID NO: 375) or the CBD of toxin B (SEQ ID NO: 376), at ~500nM was mixed with excess antibody at specified molar ratios (1:5 and 1:20; CBD:Mab) in phosphate buffered saline containing 5% glycerol pH 7.4 (PBS/G) and incubated at room temperature for 1 hour.

[0216] Any precipitation visible after 1 hr was recorded as +++ (strong), ++ (moderate), + (minimal), or – (not observed). Following centrifugation (5 min. @ 16,000 x g), the mixture of antibody and CBD was subjected to SEC analysis using a Superose 6 column (GE Healthcare) with PBS/G as the mobile phase. Protein peaks corresponding to complexes larger than the antibody or CBD alone were interpreted as binding to the C-terminal domain.

[0217] The results demonstrated that CBD binding corresponds well with that predicted from the domain of binding inferred from SPR (Biacore) and CBD studies (see example 5). One notable exception was H1H3134N, where binding to CBD-A was not observed via SEC but K_D values indicated dual binding properties for the antibody.

Table 7: Domain of binding for anti-*Clostridium difficile* toxin A and B antibodies

mAb	Precipitation with CBD-A	Observed CBD-A binding via SEC	Precipitation with CBD-B	Observed CBD-B binding via SEC	Domain Binding Via Biacore
H2M3067N	+++	Yes	NT	NT	C-Term A/B

H1M3117N	+++	Yes	NT	NT	C-Term A
H2M3121N	-	No	NT	NT	Non CBD
H2M3123N	-	No	NT	NT	Non CBD
H2M3124N	-	No	NT	NT	Non CBD
H1M3134N	-	No	NT	NT	C-Term A/B
H1H3317P	NT	NT	-	Yes	NT
H1H3324P	+	Yes	NT	NT	C-Term A
H1H3325P	-	No	NT	NT	Non CBD
H1H3328P	-	Yes	NT	NT	C-Term A
H1H3330P	-	Yes	N.D.	N.D.	C-Term A
H1H3335P	NT	NT	-	No	Non CBD
H1H3337P	NT	NT	-	No	Non CBD
H1H3339P	NT	NT	-	No	Non CBD
H1H3343P	NT	NT	-	No	Non CBD
H1H3344P	NT	NT	-	No	Non CBD
H1H3347P	NT	NT	-	No	Non CBD
H1H3350P	-	Yes	NT	NT	NT
H1H3354P	NT	NT	-	No	Non CBD

NT= Not Tested. TBD= To Be Done
Non CBD indicates no binding to C-term receptor Binding Domain of Toxin-A or -B.

Example 7. Determination of the neutralization potency of anti-*Clostridium difficile* toxin A and/or toxin B antibodies

[0218] To determine the neutralization potency (IC_{50}) of anti-*C. difficile* antibodies *in vitro*, a cell viability assay was conducted. Briefly, Vero cells ($1.25x10^3$) cultured in MEM alpha medium, supplemented with 10 % FBS, were seeded into 96-well microplates and incubated for 16-18 hours at 37°C, in 5% CO_2. Anti-*C. difficile* toxin antibodies, at various concentrations (0-66nM), were added to the cells and subsequently incubated with *C. difficile* toxin A (32 or 25pM) or toxin B (0.03pM or 0.01pM) for 48hrs. Controls not containing toxin (100% viability) and controls containing toxin but no antibody (100% relative lethality) were utilized. All dilutions of antibody were conducted in triplicate. Following the 2-day incubation, cell viability was measured by adding tetrazolium salt (WST-1; Roche Biochemicals), waiting for 4hrs to allow for color development and then recording absorbance at 450 nm. Absorbance values were analyzed by a four-parameter logistic equation over an 11-point response curve (GraphPad Prism).

[0219] The results showed that ten antibodies displayed neutralization against toxin A with IC_{50} values ranging from 7pM to 65pM at 25-32pM constant toxin A (Table 8A). Of note, H1H3330P demonstrated neutralization potency equal to that of Control III (isotype matched comparator antibody, clone 3358 as set forth in US2009/0087478) and potency of approximately 20 fold greater than control I (see US2005/0287150 for clone 3D8). Several toxin-B neutralizing antibodies showed significantly greater potency than control II (isotype matched comparator antibody, see clone 124-152 of US2005/0287150) with IC_{50}s ranging from 25-120pM at 0.03pM constant toxin B (Table 8B). Antibodies H1M3067N and H1M3134N, while able to bind both

toxin A and B showed only neutralization activity against toxin A. While the reason for this is not yet known, one possible explanation for this finding may be that while antibodies can bind at many sites in the repetitive regions of the C terminal portion of the toxin, other parts of the same toxin domain may still be capable of interacting with the mammalian membrane, thus allowing entry of the toxin into the cell.

Table 8A: Neutralization potency (IC_{50}) for selected mAbs against Toxin A

mAb	Trial 1 (IC_{50}) 32pM Toxin A	Trial 2 (IC_{50}) 32pM Toxin A	Trial 3 (IC_{50}) 32pM Toxin A	Trial 4 (IC_{50}) 32pM Toxin A	Trial 5 (IC_{50}) 25pM Toxin A
H1M3067N	64pM	44pM	NT	NT	NT
H1M3117N	29pM	11pM	NT	NT	NT
H2aM3121N	65pM	35pM	NT	NT	NT
H2aM3123N	65pM	24pM	NT	NT	NT
H2aM3124N	41pM	21pM	NT	NT	NT
HIM3134N	NT	NT	NT	38pM	NT
H1H3324P	NT	NT	NT	33pM	NT
H1H3325P	NT	NT	NT	33pM	NT
H1H3328P	NT	NT	112pM	NT	NT
H1H3330P	NT	NT	7pM	NT	7pM
Control I	NT	NT	NT	NT	199pM
Control III	18pM	6pM	10pM	11pM	9pM

NT: Not tested

Table 8B: Neutralization potency (IC_{50}) for selected Mabs against Toxin B

mAb	Trial 1 (IC_{50}) 0.1pM Toxin B	Trial 2 (IC_{50}) 0.1pM Toxin B	Trial3 (IC_{50}) 0.03pM Toxin B
H1M3067N	No Neutralization		
HIM3134N	No Neutralization		
HIH3317P	No Neutralization	NT	NT
H1H3335P	730pM	380pM	120pM
H1H3337P	1730pM	980pM	320pM
H1H3339P	480pM	270pM	90pM
H1H3343P	280pM	200pM	50pM
H1H3344P	580pM	400pM	40pM
H1H3347P	130pM	90pM	25pM
H1H3350P	No Neutralization	NT	NT
H1H3340P	NT	No Neutralization	NT
H1H3411P	NT	8pM#	NT
Control II	1800pM	1500pM	290pM

Antibody only partially protect (40-50%) at highest concentration
NT: Not Tested

Example 8. Generation of a Bi-specific Antibody

[0220] Various bi-specific antibodies are generated for use in practicing the methods of the invention. For example, *C. difficile* toxin A or toxin B-specific antibodies are generated in a bi-specific format (a "bi-specific") in which variable regions binding to distinct domains of toxin A and/or B are linked together to confer dual-domain and/or dual toxin specificity within a single binding molecule. Appropriately designed bi-specifics may enhance overall toxin neutralization efficacy through increasing both specificity and binding avidity. Variable regions with specificity for individual domains, as shown in Figure 1, (*e.g.*, segments of the N-terminal domain, which is the glucosylating enzymatic domain (designated as domain 'A'), or the autocatalytic processing domain (designated as domain 'C'), or the translocating domain (designated as domain 'D'), or the carboxy terminal receptor binding domain (designated as domain 'B') or that can bind to different regions within one domain, are paired on a structural scaffold that allows each region to bind simultaneously to the separate epitopes, or to different regions within one domain. In one example for a bi-specific, heavy chain variable regions (V_H) from a binder with specificity for one domain are recombined with light chain variable regions (V_L) from a series of binders with specificity for a second domain to identify non-cognate V_L partners that can be paired with an original V_H without disrupting the original specificity for that V_H. In this way, a single V_L segment (*e.g.,* V_L1) can be combined with two different V_H domains (*e.g.,* V_H1 and V_H2) to generate a bi-specific comprised of two binding "arms" (V_H1- V_L1 and V_H2- V_L1). Use of a single V_L segment reduces the complexity of the system and thereby simplifies and increases efficiency in cloning, expression, and purification processes used to generate the bi-specific (See, for example, USSN13/022759 and US2010/0331527).

[0221] Alternatively, antibodies that bind both toxin A and/or toxin B and a second target, such as, but not limited to, for example, a second different anti-toxin A or anti-toxin B antibody, or a toxoid, or a vaccine, may be prepared in a bi-specific format using techniques described herein, or other techniques known to those skilled in the art. Antibody variable regions binding to distinct toxin A regions may be linked together with variable regions that bind to relevant sites on, for example, toxin B, to confer dual-antigen specificity within a single binding molecule. Appropriately designed bi-specifics of this nature serve a dual function. For example, in the case of a bi-specific antibody that binds both toxin A and toxin B, one may be able to better neutralize both toxin A and toxin B concurrenty, without the need for administration of a composition containing two separate antibodies. Variable regions with specificity for toxin A, are combined with a variable region with specificity for toxin B and are paired on a structural scaffold that allows each variable region to bind to the separate antigens.

[0222] The bi-specific binders are tested for binding and functional blocking of the target antigens, for example, toxin A and toxin B, in any of the assays described above for antibodies. For example, standard methods to measure soluble protein binding are used to assess the bispecific interaction, such as Biacore, ELISA, size exclusion chromatography, multi-angle laser

light scattering, direct scanning calorimetry, and other methods. Binding of bi-specific antibodies to both toxin A and toxin B is determined through use of an ELISA binding assay in which synthetic peptides representing the different toxins are coated onto the wells of microtiter plates, and binding of a bi-specific is determined through use of a secondary detection antibody. Binding experiments can also be conducted using surface plasmon resonance experiments, in which real-time binding interaction of peptide to antibody is measured by flowing a peptide or bi-specific across a sensor surface on which bi-specific or peptide, respectively, is captured. Functional *in vitro* blocking of both toxin A and toxin B by a bi-specific is determined using any bioassay such as the neutralization assay described herein, or by *in vivo* protection studies in appropriate animal models, such as those described herein.

Example 9. Evaluation of *in vivo* Efficacy of Anti-Toxin A and/or Anti-Toxin B Antibodies against *C. difficile* Infection (CDI) in a Hamster Relapse Model (A) and in an Acute Hamster Model (B)

[0223] The efficacy of antibodies specific for toxin A and/or toxin B from *C. difficile* against infection with *C. difficile* was evaluated in hamsters in two different models, described below. Hamsters, in the presence of clindamycin, are sensitive to *C. difficile* infection and usually die within 2-4 days after infection.

[0224] (A) Relapse model: Male Syrian Golden Hamsters were given an oral suspension containing a mixture of *C. difficile* spores and vegetative cells (10^6 in total) on day -1. Twenty-four hours after infection (day 0), animals received a single subcutaneous injection of clindamycin (10 mg/kg). On days 1-3, hamsters were administered oral vancomycin (10 mg/kg) once per day to ameliorate the infection. The antibiotic vancomycin is used clinically to treat a *C. difficile* infection. After the last vancomycin dose, antibodies were administered subcutaneously q.d. for 4 days (days 3-6), or 1 day (day 3) according to their treatment and dosing group (see Tables 9A and 9B below).

[0225] Two different trials (See Figures 2 and 3) using the relapse model as a surrogate for clinical efficacy were conducted. Both trials compared two antibody combinations:

1. Antibodies designated H1H3330P and H1H3347P
2. Comparator anti-Toxin A (Control I; See US patent 7625559 for clone 3D8 sequence) and comparator anti-Toxin B antibodies (Control II; See US patent 7625559 for clone 124-152 sequence)

[0226] In Trial 1, four doses of antibody were administered at 5 mg/kg of each antibody (a total 10 mg/kg dose). In Trial 2, one dose of antibody was given at either 5 mg/kg or 2 mg/kg of each antibody (a total of either 10mg/kg or 4 mg/kg).

Table 9A Trial 1 Design: Relapse model: Combination Treatments with H1H3330P + H1H3347P or comparator anti-Toxin A + comparator anti-Toxin B

Group	Treatment*	Dose (mg/kg x # doses)	*n*
1	Negative Control (irrelevant) antibody	10 x 4	14
2	Comparator anti-Toxin A and comparator anti-Toxin B	[5/5] x 4	23
3	(H1H3330P + H1H3347P combination)	[5/5] x 4	23
4	No antibody		15

* All animals received vancomycin as noted above.

Table 9B Trial 2 Design: Relapse model: Combination Treatments with H1H3330P + H1H3347P or comparator anti-Toxin A + comparator anti-Toxin B

Group	Treatment*	Dose (mg/kg x # doses)	*n*
1	Negative Control (irrelevant) antibody	10 x 1	14
2	Comparator anti-Toxin A and comparator anti-Toxin B	[5/5] x 1	16
3	(H1H3330P + H1H3347P combination)	[5/5] x 1	16
4	Comparator anti-Toxin A and comparator anti-Toxin B	[2/2] x 1	16
5	(H1H3330P + H1H3347P combination)	[2/2] x 1	16

* All animals received vancomycin as noted above.

[0227] Animals were observed twice a day for the duration of the experiment. General observations included signs for mortality and morbidity, the presence of diarrhea ("wet tail") and overall appearance (activity, general response to handling, touch, ruffled fur). Animals judged to be in a moribund state were euthanized. Criteria used to assign a moribund state were extended periods (5 days) of weight loss, progression to an emaciated state, prolonged lethargy (more than 3 days), signs of paralysis, skin erosions or trauma, hunched posture, and a distended abdomen. Observations continued, with deaths or euthanasia recorded for a period up to 18 days post-infection for the relapse model.

[0228] (**B**) **Acute model:** Male Syrian Golden Hamsters were treated with clindamycin intraperitoneally at a dose of 10 mg/kg on day -1. On day 0 *C. difficile* spores were diluted with sterile PBS to give 100 spores /300 µl and administered by oral gavage. Antibodies were administered every day for 4 days, beginning on day -3 and continuing to day 0, using a subcutaneous route. The dose of the antibodies is indicated in the figure legend. See also Table 9C below for the study outline.

Table 9C Trial 3: Acute model: Combination Treatments with H1H3330P + H1H3347P at various doses

Group	Treatment	Dose (mg/kg x # doses)	# Animals
1	Uninfected control	-	5
2	Infected control	PBS x 4	10
3	Negative Control (irrelevant) antibody	[100] x 4	14
4	(H1H3330P + H1H3347P combination)	[50/50] x 4	14
5		[16/16] x 4	14
6		[5.5/5.5] x 4	14
7		1.85/1.85 x 4	14

Table 9D Trial 4: Acute model: Combination Treatments with H1H3330P + H1H3347P at various doses

Group	Treatment	Dose (mg/kg x # doses)	# Animals
1	Uninfected control	-	5

2	Infected control	PBS x 4	10
3	Negative Control (irrelevant) antibody	[100] x 4	14
4	(H1H3330P + H1H3347P combination)	[20/20] x 4	14
5		[5/5] x 4	14
6	Comparator anti-Toxin A and comparator anti-Toxin B	[20/20] x 4	14
7		[5/5] x 4	14

[0229] Animals were observed twice a day for the duration of the experiment. General observations included signs for mortality and morbidity, the presence of diarrhea ("wet tail") and overall appearance (activity, general response to handling, touch, ruffled fur). Animals judged to be in a moribund state were euthanized. Criteria used to assign a moribund state were extended periods (5 days) of weight loss, progression to an emaciated state, prolonged lethargy (more than 3 days), signs of paralysis, skin erosions or trauma, hunched posture, and a distended abdomen. Observations continued, with deaths or euthanasia recorded for a period up to10 days for the acute model.

Results

[0230] Statistical analysis of data from hamster models was done using the Log-Rank (Mantel Cox) test. For pairwise comparisons the Bonferroni correction was applied to the critical *P* value.

[0231] In the first trial, which was a multi-dose study using a hamster relapse model, (see Figure 2), combination treatment with H1H3330P plus H1H3347P, or combination treatment with the comparator antibodies, showed an increase in overall survival vs isotype control, or vancomycin alone, (74-78%; combination of anti-toxin A and anti-toxin B antibodies vs 27-43 %; control arms). Specifically, by day 19, 27% of the hamsters receiving PBS alone survived; 43% receiving the isotype control survived; 74% receiving the anti-toxin A plus anti-toxin B comparator antibody combination survived; and 78% receiving the H1H3330P (anti-A antibody) plus H1H3347P (anti-B antibody) combination survived.

[0232] In the second trial, which was a single-dose study using a hamster relapse model (see Figure 3), combination treatment with either H1H3330P plus H1H3347P, or the comparator

antibodies, increased survival as compared to the isotype control (negative control antibody), although there was no discrimination between the 2 mg/kg and 5 mg/kg doses.

[0233] In the first acute model study in hamsters (See Figure 4), treatment with the H1H3330P plus H1H3347P combination showed significant protection of the hamsters from death in a titratable manner compared to the negative controls ($p<0.0001$ for all groups vs isotype controls). The doses titrated from 50 mg/kg to 1.85 mg/kg (of each antibody given as a combination), with the high dose providing protection for all of the animals until day 7 compared to day 1 for the lowest dose.

[0234] In further studies using the acute hamster model (see figure 5), combination treatment with either H1H3330P plus H1H3347P, or a combination of the comparator antibodies, significantly increased survival as compared to the isotype control (Figure 5; Isotype control at 40 mg/kg vs Control I/Control II at 20 mg/kg each, $p<0.0001$; isotype control at 40 mg/kg vs Control I/Control II at 5 mg/kg each, $p=0.0003$; isotype control at 40 mg/kg vs H1H3330P/H1H3347P at 20 mg/kg each, $p<0.0001$; isotype control at 40 mg/kg vs H1H3330P/H1H3347P at 5 mg/kg each, $p<0.0001$). However, treatment with a combination of H1H3330P plus H1H3347P protected the hamsters from death in a manner superior to comparator antibody controls when tested at the low dose of 5 mg/kg of each antibody ($p<0.0001$), whereas there was no significant difference between the combination of H1H3330P plus H1H3347P vs the combination of the comparator antibodies at the higher dose of 20 mg/kg of each antibody ($p=0.73$). This result clearly demonstrates superiority at a low dose in the acute hamster model and suggests that doses of the H1H3330P plus H1H3347P antibodies could be effective in the clinic at lower concentrations compared to the comparator antibodies.

Example 10. The Effect of Anti-Toxin A and Anti-Toxin B Antibodies on Blocking the Cytotoxicity Induced by Culture Supernatant from Several Group BI Hypervirulent *C. difficile* Strains: Comparison with Comparator mAbs

[0235] Patients infected with clinically-hypervirulent BI/NAP1/027 strains have lower cure rates than patients infected with non-BI strains when treated with either fidaxomicin or vancomycin (Petrella, LA, *et al.* (2012), Clinical Infectious Diseases, 55(3): 351-357). Furthermore, BI/NAP1/027 strains are associated with a higher CDI recurrence rate and higher expected mortality rate when compared to prototypic strains (Loo, VG, *et al.* (2005), N Engl J Med, 353:23; Petrella, LA, *et al.* (2012), Clinical Infectious Diseases, 55(3): 351-357. These hypervirulent strains are characterized by an increase in toxin A and B production, the presence of binary toxin and increased resistance to fluoroquinolones. The increase in toxin A and B production is most likely caused by a loss-of-function mutation in *tcdC*, a putative negative regulator of *tcdA* and *tcdB* expression, resulting in sustained toxin production throughout the lifecycle.

[0236] The ability of a 1:1 molar ratio mix of H1H3330P and H1H3347P to neutralize toxin from four clinically-isolated *C. difficile* BI/NAP1/027 strains was tested in a cell-based neutralization assay. The VA5 and VA17 clinically isolated hypervirulent strains were obtained from Case Western Reserve University, Cleveland, OH. The 6336 and 6443 clinically isolated hypervirulent strains were obtained from the Dept. of Veterans Affairs, Edward Hines, Jr. Hospital, Hines, IL. Neutralization assays utilized Vero cells, a monkey kidney epithelial cell line, due to their susceptibility to both *C. difficile* toxins. Cells were incubated with varying amounts of antibody cocktail and a fixed amount of culture supernatant isolated from several *C. difficile* strains for 48 hours. Cytotoxicity was determined by addition of WST-1 reagent, a redox indicator that yields a colorimetric change when reduced; metabolic activity during cell growth reduces WST-1, resulting in increased absorbance at 450 nm.

[0237] Culture supernatant from several clinically isolated BI strains exhibited a wide range of cytotoxic activity on Vero cells, with EC_{50} values for inducing cell cytotoxicity ranging from a 3700-fold dilution for the VA5 strain to 88200-fold dilution for the 6443 strain. A 1:1 molar ratio mix of H1H3330P and H1H3347P blocked cytotoxicity induced by culture supernatants from all group BI strains tested with a more than 34-fold better neutralization potency compared to a 1:1 molar ratio mix of comparator anti-Toxin A (control I; See US patent 7625559 for clone 3D8 sequence) and comparator anti-Toxin B (control II; See US patent 7625559 for clone 124-152 sequence). These data demonstrate that the H1H3330P/H1H3347P antibody pair was able to neutralize culture cytotoxicity with IC_{50} values in the picomolar range (31-45pM) for tested hypervirulent BI strains, compared to the comparator mAb cocktail (IC_{50} range: 1200-1700pM; see Table 10).

Table 10

Strain	EC_{50} (Fold Dilution)	Neutralization Assay			
		[Supernatant] (Fold Dilution)	H1H3330P/ H1H3347P IC_{50} (pM)	Comparator mAb 1/2 IC_{50} (pM)	Fold pair/control
VA5	6900	4700	36	1400	39
VA17	3700	3000	31	1400	45
6336	15200	12100	45	1700	38
6443	88200	57500	35	1200	34

Example 11. Epitope mapping of the anti-toxin A antibody H1H3330P

[0238] The epitope of the C-term receptor-Binding Domain (CBD) of toxin A (SEQ ID:375) bound by H1H3330P was determined using mass spectrometry based proteomics. Briefly, the CBD of toxin A was subjected to trypsin digestion over a 12 hour period and the samples run on 10-14% gradient SDS-PAGE, followed by transfer to nitrocellulose membranes and Western

blot analysis using either the H1H3330P antibody, or the control I antibody (See US patent 7625559 for 3D8 antibody sequence) as primary antibodies. Further analysis of the peptide sequences that bound to the H1H3330P antibody was done using 2D electrophoresis followed by MALDI-TOF MS analysis. The procedures are described in greater detail below.

Limited trypsin digestion of Toxin A

[0239] Recombinant C-term receptor-Binding Domain (CBD) of toxin A (0.4 µg/µl in PBS) was added with sequence grade modified trypsin (Promega, Cat # V511C) at a 1:80 mass ratio and incubated at 37°C for 0-12 hr. The enzyme was inactivated by adding 2 volumes of 1X Laemmli sample buffer and heated at 95°C for 5 min. The samples were stored at -20°C until analysis.

Western blot analysis

[0240] The extent of the proteolysis was first examined by 10-14% gradient SDS-PAGE. The amount of each sample loaded was equivalent to 1 µg initial CBD of Toxin A, and the separated proteins in the gel were visualized with SimplyBlue coomassie stain (Invitrogen, Cat# LC6065).

[0241] The samples digested for 0 hour and 12 hour were then selected for 10-14% gradient SDS-PAGE separation with an equivalent to 50 ng initial CBD of toxin A loaded for each sample. Separated proteins were transferred to a nitrocellose membrane, and probed with primary antibody H1H3330P or Control Antibody I at a concentration of 1 µg/ml in TBST (Tris-buffer saline solution containing 0.05% Tween-20) overnight at 4°C followed by anti-human IgG HRP conjugated secondary antibody (Pierce, Cat # 31412; at 1:15,000 dilution in TBST). Both H1H3330P & Control 1 antibodies had a human IgG1 constant domain. The membrane was incubated with chemiluminescence substrate (Perkin Elmer, Cat # NEL103E001EA) and the image was captured onto X-ray film.

2D Gel Electrophoresis

[0242] To determine which amino acids were represented in the protein band unique to Western blots performed using the H1H3330P antibody, a two-dimensional (2D) gel was performed using the 12 hour trypsin digest of the CBD of toxin A.

In-gel trypsin digestion and peptide mapping by MALDI-TOF MS

[0243] The 2D-gel analysis revealed 4 protein spots, closely clustered in the pH (pI values ~ 9) dimension, which composed the 50kDa band that was visualized by Western blot using H1H3330P. The 4 protein spots with corresponding molecular weights of ~50 kDa from the 2D-gel using the 12 hour trypsin digestion were excised, destained by 50% acetonitrile, reduced by 65 mM DTT, and alkylated by 135 mM iodoacetamide. After dehydration by acetonitrile, 20 ul of

2.5 ng/µl sequence grade trypsin (Promega, Cat # V5111) was added to cover the gel bands and the in-gel digestion was carried out by overnight incubation at 37°C.

[0244] The resulting peptides were desalted by Ziptip C18 (Millipore, Cat# ZTC18S096) and analyzed by Bruker UltrafleXtreme MALDI-TOF-TOF MS. The spectrum was processed by FlexAnalysis software and internally calibrated with autolytic trypsin fragment peaks. The calibrated peak lists were searched against an in-house database containing the sequence of the CBD Toxin A at a mass accuracy of 10 ppm.

Results

[0245] The results showed that blotting with H1H3330P revealed a major protein band at around 50kDa at 12 hours post trypsin digestion, while no protein band having a molecular weight of around 50kDa was observed when blotting was carried out with the control 1 antibody at 12 hours post trypsin digestion.

[0246] To determine which amino acids were represented in the 50kDa protein band, unique to Western blots performed using H1H3330P, a two-dimensional (2D) gel was performed using the 12 hour trypsin digest, as described above. As noted, 2D-gel analysis revealed 4 protein spots, closely clustered in the pH (pI values ~ 9) dimension, which composed the 50kDa band visualized by Western blot using H1H3330P. Mass spectrometry analysis of these 4 protein spots identified 17 matching peptides covering amino acid residues 468-863 of the CBD of toxin A (SEQ ID: 375). This fragment of toxin A (amino acids spanning residue 468 to 863) has a predicted molecular weight of 45 kDa and a predicted isoelectric point of 9.01 corresponding well to the values obtained from 2-D gel analysis.

[0247] This example illustrates that the anti-toxin A antibody H1H3330P has an epitope unique from that of Control 1 (3D8 in US 7625559) and binds the CBD of toxin A within amino acids 468 to 863. Particular amino acid sequences were identified within this region which interacted with the H1H3330P antibody and these amino acid sequences were residues 468-488 of SEQ ID NO: 375, residues 510-530 of SEQ ID NO: 375, residues 602-610 of SEQ ID NO: 375, residues 644-703 of SEQ ID NO: 724-794 of SEQ ID NO: 375, residues 799-814 of SEQ ID NO: 375 and residues 858-863 of SEQ ID NO: 375.

[0248] Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

What is claimed is:

1. An isolated antibody or an antigen-binding fragment thereof that specifically binds to *Clostridium difficile* toxin B, comprising the HCDR1, HCDR2 and HCDR3 contained within a HCVR amino acid sequence selected from SEQ ID NOs: 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338 and 354; and the LCDR1, LCDR2 and LCDR3 contained within a LCVR amino acid sequence selected from SEQ ID NOs: 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346 and 362.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises: (a) a HCVR having the amino acid sequence of SEQ ID NO: 274; and (b) a LCVR having the amino acid sequence of SEQ ID NO: 282.

3. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the isolated antibody or antigen-binding fragment thereof comprises: a HCVR/LCVR amino acid sequence pair selected from SEQ ID NOs: 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340 and 356;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342 and 358;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344 and 360;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348 and 364;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350 and 366; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352 and 368.

5. The isolated antibody or an antigen-binding fragment thereof of any one of claims 1 to 4, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 276,

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 278;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 280;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 284;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 286; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 288.

6. A pharmaceutical composition comprising one or more antibodies of any one of claims 1 to 5 and a pharmaceutically acceptable carrier or diluent.

7. The pharmaceutical composition of claim 6, further comprising an antibody, or an antigen-binding fragment thereof that binds specifically to toxin A of *Clostridium difficile*.

8. The pharmaceutical composition of claim 7, wherein:

the antibody or antigen-binding fragment thereof that binds specifically to toxin A comprises the three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) amino acid sequences selected from SEQ ID NOs: 2, 98, 114, 130, 146 and 162; and the three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) amino acid sequences selected from SEQ ID NOs: 10, 106, 122, 138, 154 and 170.

9. The pharmaceutical composition of claim 7 or 8, wherein the antibody or an antigen-binding fragment thereof that specifically binds toxin A of *Clostridium difficile* comprises a HCVR/LCVR amino acid sequence pair of SEQ ID NO: 146/154.

10. The pharmaceutical composition of any one of claims 7 to 9, comprising:

a) an isolated first antibody or antigen-binding fragment thereof that specifically binds toxin A of *Clostridium difficile*,

b) an isolated second antibody or antigen-binding fragment thereof that specifically binds toxin B of *Clostridium difficile*, and

c) a pharmaceutically acceptable carrier or diluent.

11. The pharmaceutical composition of any one of claims 7 to 10, wherein the antibodies contained within the composition are effective at neutralizing toxins A and B from a hypervirulent strain of *Clostridium difficile*.

12. The pharmaceutical composition of claim 11, wherein the hypervirulent strain of *Clostridium difficile* is a BI/NAP1/027 strain.

13. The pharmaceutical composition of claim 12, wherein the BI/NAP1/027 strain is selected from VA5, VA17, 6336 and 6443.

14. A method for treating a patient suffering from a *Clostridium difficile*-associated condition or disease, or for treating at least one symptom or complication associated with the condition or disease, or for preventing the development of a *Clostridium difficile*-associated condition or disease in a patient at risk thereof, the method comprising administering to the patient an effective amount of the isolated antibody or antigen-binding fragment thereof according to any one of claims 1 to 5, or the pharmaceutical composition according to any one of claims 6 to 13, wherein the *Clostridium difficile*-associated condition or disease is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the condition or disease is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of recurrences, or relapses with *Clostridium difficile* is reduced.

15. The method of claim 14, wherein the at least one symptom or complication associated with the *Clostridium difficile*-associated condition or disease is selected from the group consisting of anorexia, abdominal pain, abdominal bloating, diarrhea with or without bleeding, dehydration, malnutrition, pseudomembranous colitis, complete or segmental colonic resection, fever and systemic infection (sepsis), death, relapse of the *Clostridium difficile* condition or disease, and rejection of a transplanted tissue or organ.

16. The method of claim 14 or 15, wherein the patient at risk of developing a *Clostridium difficile*-associated condition or disease is selected from the group consisting of an elderly patient (≥ 65 years old), a patient who is immunocompromised due to underlying illness or due to administration of immunosuppressive therapeutics, a patient who has some underlying medical condition that may pre-dispose them to acquiring a *Clostridium difficile* infection, a patient hospitalized for an extended period of time (at least one week), a patient who has been treated for an extended period of time(≥ 14 days) with broad spectrum antibiotics, a cancer patient, a transplant patient, and a patient on therapy with agents such as but not limited to a proton pump inhibitor, or histamine H2 receptor inhibitor that are used

for treatment of gastrointestinal diseases or conditions to reduce or treat gastric acidity, gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, or heartburn.

17. The pharmaceutical composition of any one of claims 6 to 13 for use in treating a patient suffering from a *Clostridium difficile*-associated condition or disease, or for treating at least one symptom or complication associated with the condition or disease, or for preventing the development of a *Clostridium difficile*-associated condition or disease in a patient at risk thereof, wherein the *Clostridium difficile*-associated condition or disease is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the condition or disease is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of recurrences, or relapses with *Clostridium difficile* is reduced.

18. Use of the isolated antibody or antigen-binding fragment thereof according to any one of claims 1 to 5 or the pharmaceutical composition of any one of claims 6 to 13 in the manufacture of a medicament for use in treating a patient suffering from a *Clostridium difficile*-associated condition or disease, or for treating at least one symptom or complication associated with the condition or disease, or for preventing the development of a *Clostridium difficile*-associated condition or disease in a patient at risk thereof, wherein the *Clostridium difficile*-associated condition or disease is either prevented, or lessened in severity and/or duration, or at least one symptom or complication associated with the condition or disease is prevented, or ameliorated, or that the frequency and/or duration of, or the severity of recurrences, or relapses with *Clostridium difficile* is reduced.

19. The pharmaceutical composition according to claim 17, the method according to any one of claims 14 to 16, or use according to claim 18, wherein the patient at risk of developing a *Clostridium difficile*-associated condition or disease is selected from an elderly patient, a patient who is immunocompromised due to illness or due to administration of immunosuppressive therapeutics, a patient who has some underlying medical condition that may pre-dispose them to acquiring a *Clostridium difficile* infection, a patient hospitalized for an extended period of time, a patient who has been treated for an extended period of time with broad spectrum antibiotics, a patient on therapy with a proton pump inhibitor for treatment of gastrointestinal diseases or conditions, a cancer patient, and a transplant patient.

20. The pharmaceutical composition, method or use according to claim 19, wherein the cancer patient is undergoing treatment with an anti-cancer drug, or undergoing radiotherapy to treat a cancer.

21. The pharmaceutical composition, method or use according to claim 19, wherein the transplant patient is a patient receiving a hematopoietic stem cell transplant, or a solid tissue or organ transplant.

22. The pharmaceutical composition, method or use according to claim 19 or 21, wherein the transplant patient is being treated with an immunosuppressive drug, or any transplant rejection drug, or who is undergoing treatment with a drug regimen to prevent tissue or organ graft rejection following the transplant.

23. The pharmaceutical composition according to any one of claims 7 to 13, the method according to any one of claims 14 to 16, or use according to claim 18, wherein the pharmaceutical composition is administered to the patient in combination with a second therapeutic agent.

24. The pharmaceutical composition, method or use according to claim 23, wherein the second therapeutic agent is selected from a toxoid, a *Clostridium difficile* vaccine, an antibiotic, another different antibody to *Clostridium difficile* toxin A and/or B, and any other palliative therapy useful for ameliorating at least one symptom associated with a *Clostridium difficile*-associated condition or disease.

25. The pharmaceutical composition, method or use according to claim 24, wherein the at least one symptom or complication associated with the *Clostridium difficile*-associated condition or disease is selected from the group consisting of anorexia, abdominal pain, abdominal bloating, diarrhea with or without bleeding, dehydration, malnutrition, pseudomembranous colitis, complete or segmental colonic resection, fever and systemic infection (sepsis), death, relapse of the *Clostridium difficile* condition or disease, and rejection of a transplanted tissue or organ.

26. An isolated nucleic acid encoding an antibody contained within any one of claims 1 to 5 comprising at least one non-natively occurring regulatory element.

27. An expression vector comprising the nucleic acid of claim 26.

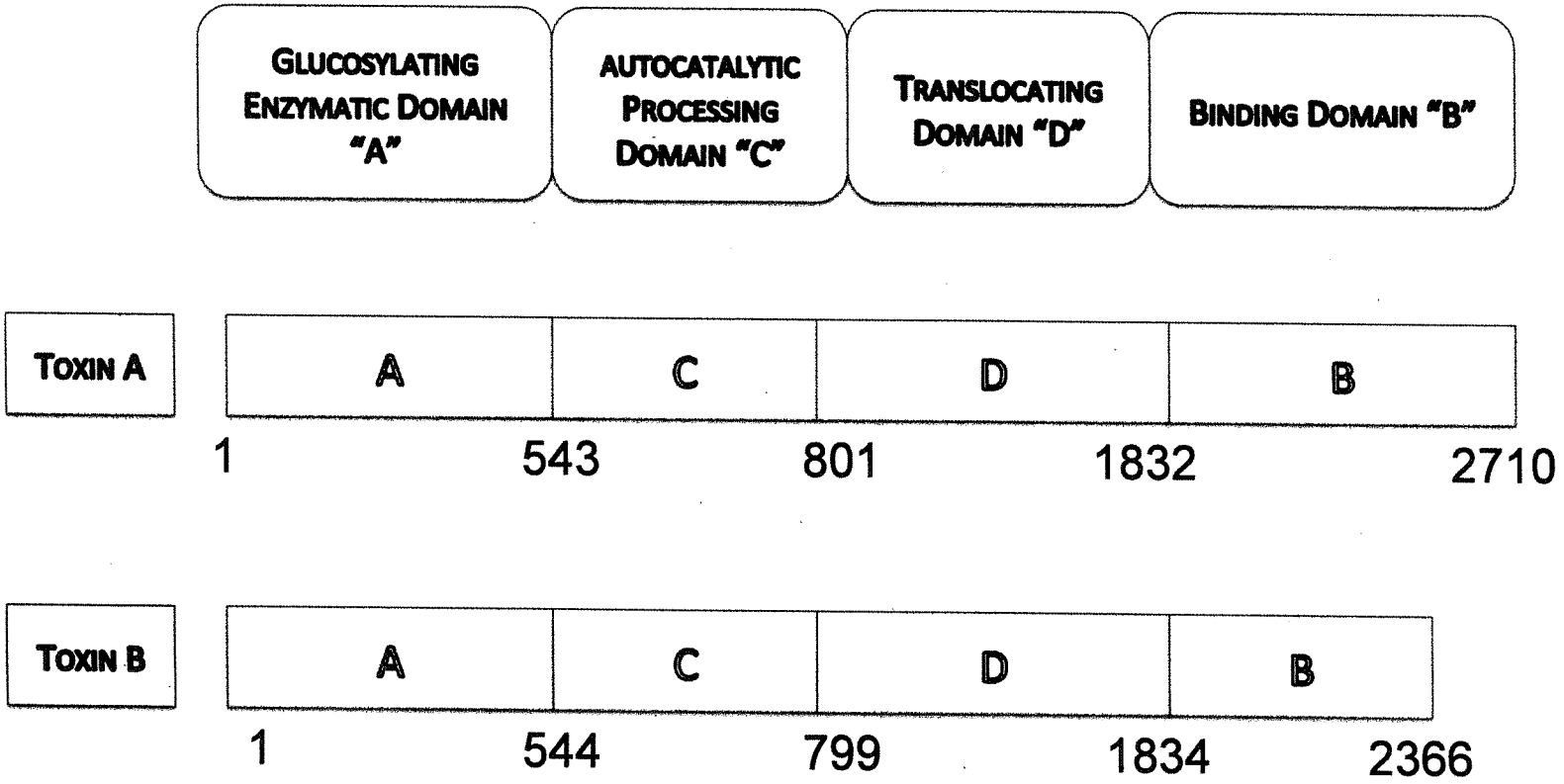
28. An isolated host cell comprising the expression vector of claim 27.

REGENERON PHARMACEUTICALS, INC.

WATERMARK PATENT AND TRADE MARKS ATTORNEYS

P37419AU01

Figure 1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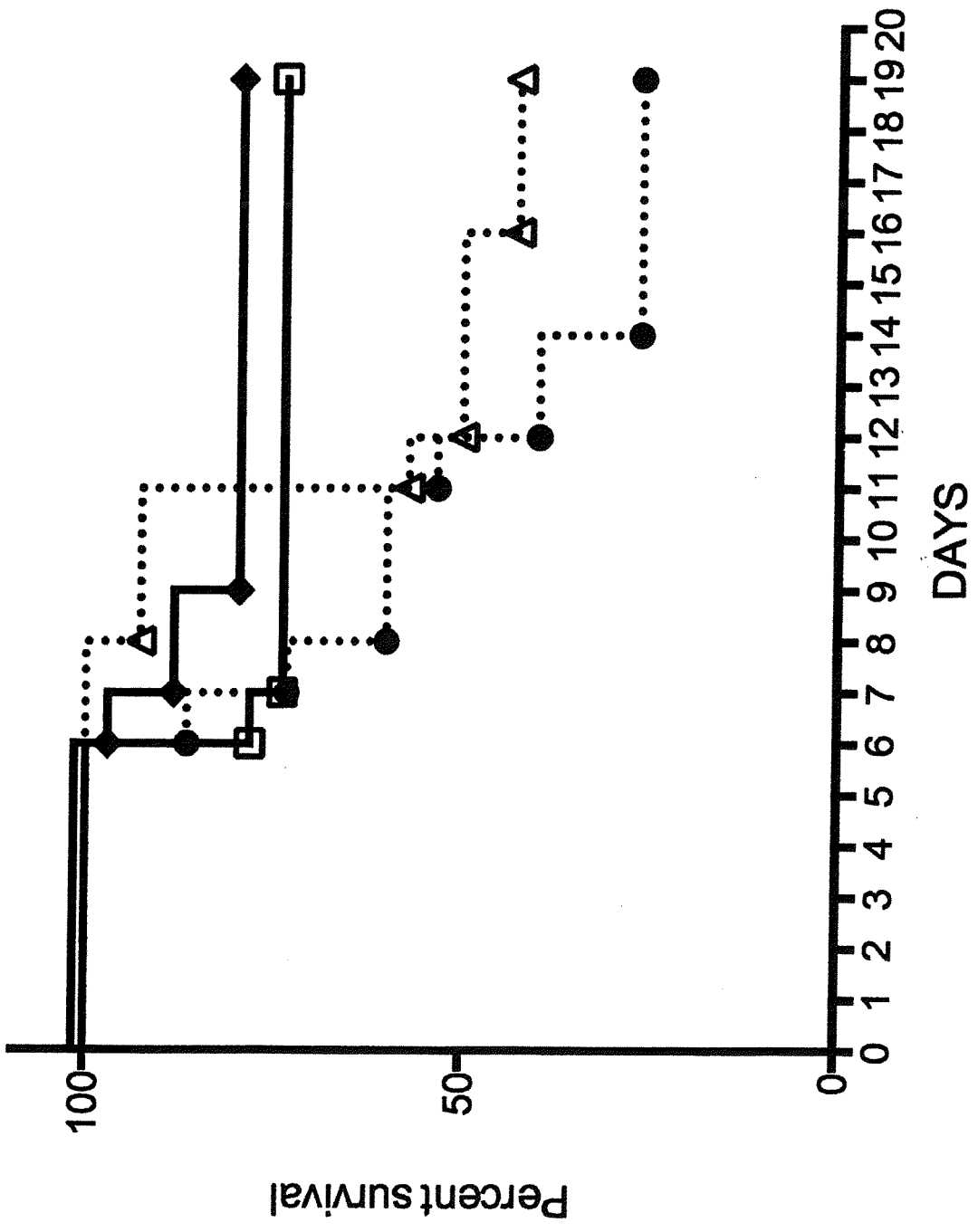

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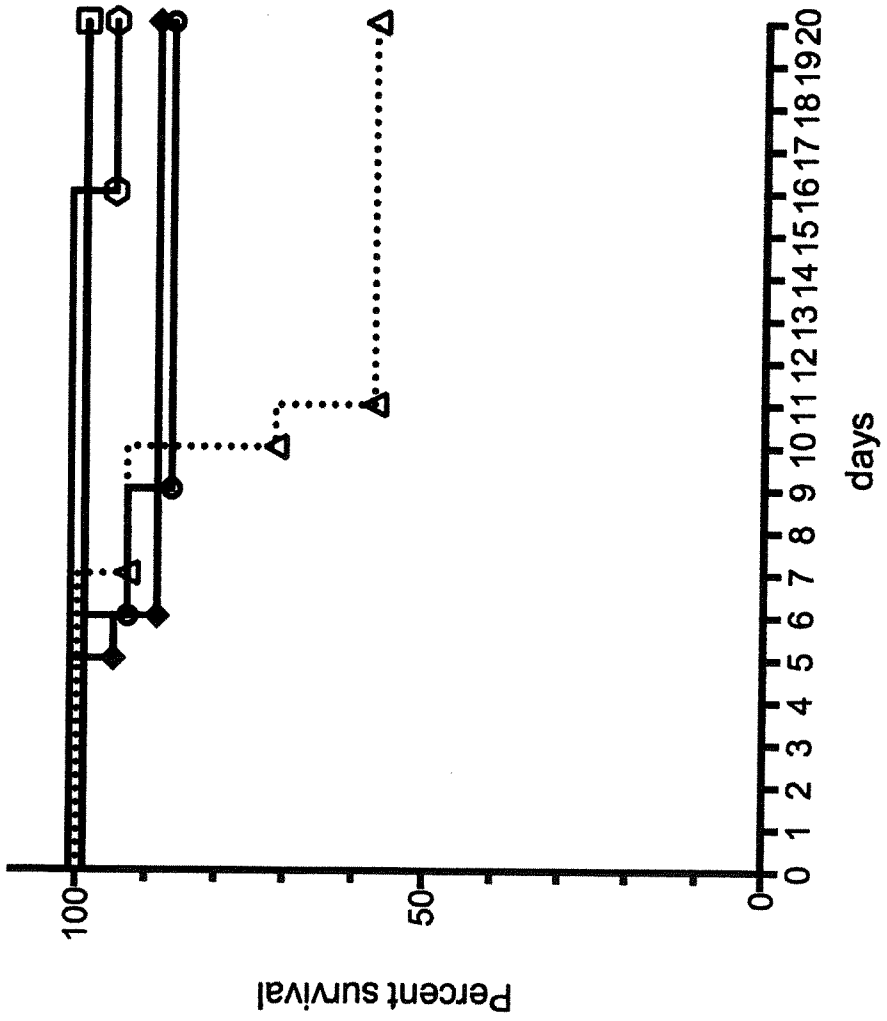

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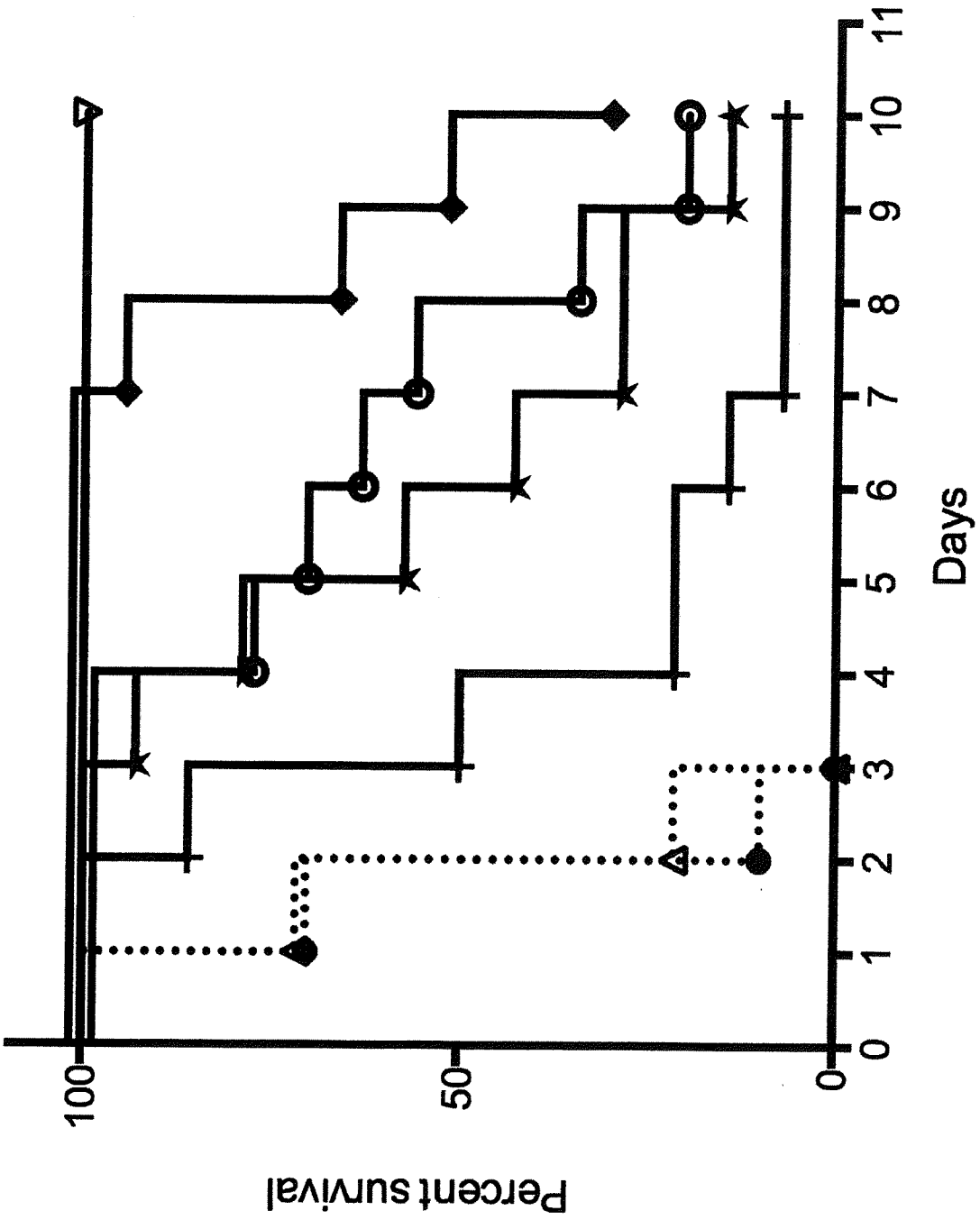

Figure 4

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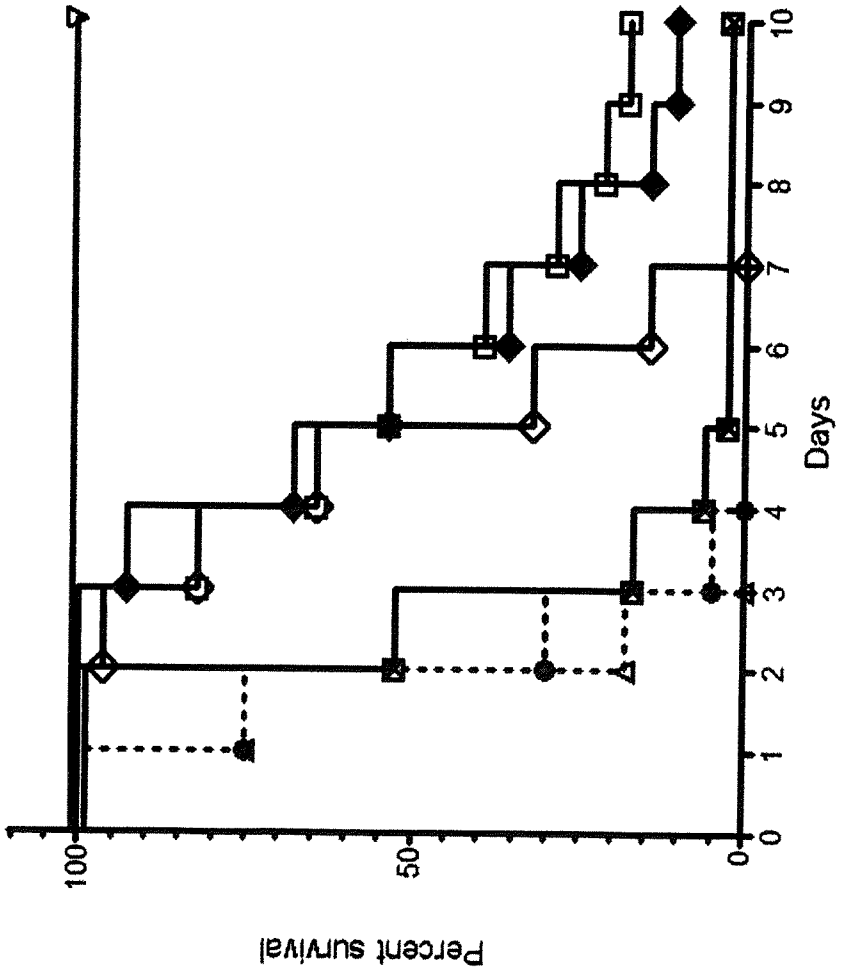

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<213> Artificial Sequence

<220>
<223> Synthetic

<400> 14
Gly Thr Ser
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<210> 15
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 15
caacagtatg gtaactcact gtacact 27

<210> 16
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 16
Gln Gln Tyr Gly Asn Ser Leu Tyr Thr
1 5

<210> 17
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 17
caggtacaac tggtggaatc tgggggagac gtggttcagc ctgggaggtc cctgagactc 60
tcctgtgcag catctggatt caccttcagt ggccacggca tgcactgggt ccgccaggct 120
ccaggcaagg gtctagagtg ggtggcactt atattgtatg atggaagtag tgaagactat 180
acagactccg tgaagggccg ctttaccgtc tccagagaca attccaagaa caccctgtat 240
ttgcaaatga acagtctgag agccgaagac acggctgtct attactgtgc gcgagggagt 300
attttaaatc gcccgtttga ttactggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 18
<211> 119
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 18
Gln Val Gln Leu Val Glu Ser Gly Gly Asp Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly His
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Leu Ile Leu Tyr Asp Gly Ser Ser Glu Asp Tyr Thr Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Ser Ile Leu Asn Arg Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 19
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 19
ggattcacct tcagtggcca cggc 24

<210> 20
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 20
Gly Phe Thr Phe Ser Gly His Gly
1 5

<210> 21
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 21
atattgtatg atggaagtag tgaa 24

<210> 22
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 22
Ile Leu Tyr Asp Gly Ser Ser Glu
1 5

<210> 23
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 23
gcgcgaggga gtattttaaa tcgcccgttt gattac 36

<210> 24
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 24
Ala Arg Gly Ser Ile Leu Asn Arg Pro Phe Asp Tyr
1 5 10

<210> 25
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 25
gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtatttta ttcagttcca acaataagat ctacttagct 120
tggttccagc agaaaccagg acagcctcct aaactactca tttactggac atctacccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcact 240
atcagtagtc tgcaggctga agatgtggca gtttactact gtcaacaata ttatactctt 300
ccattcactt tcggccctgg gaccaaagtg gatatcaaa 339

<210> 26
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 26
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Ile Leu Phe Ser
20 25 30
Ser Asn Asn Lys Ile Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Thr Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95
Tyr Tyr Thr Leu Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
100 105 110
Lys

<210> 27
<211> 36

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 27
cagagtattt tattcagttc caacaataag atctac 36

<210> 28
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 28
Gln Ser Ile Leu Phe Ser Ser Asn Asn Lys Ile Tyr
 1 5 10

<210> 29
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 29
tggacatct 9

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

<220>
<223> Synthetic

<400> 30
Trp Thr Ser
 1

<210> 31
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 31
caacaatatt atactcttcc attcact 27

<210> 32
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 32
Gln Gln Tyr Tyr Thr Leu Pro Phe Thr
 1 5

<210> 33
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 33
cagatacagc tggtggagtc tgggggaggc gtggtccagc ctggaaggtc cctgagactc 60
tcctgtgtag cctctgggtt caccctcagt ggacatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcattt atatcatttg atggaggtca tcaagactac 180
acagacgccg cggagggccg attcaccatc tccagagaca attccaagaa cacgttgtat 240
ctggaaatgg tcagcctgag acctgcagac acggctatat attattgtgt gaaagggagc 300
gactcgtcgc gaggttttgg ctactggggc cggggaatcc tggtcaccgt ctcctca 357

<210> 34
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 34
Gln Ile Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Leu Ser Gly His
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Phe Ile Ser Phe Asp Gly Gly His Gln Asp Tyr Thr Asp Ala Ala
50 55 60
Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Glu Met Val Ser Leu Arg Pro Ala Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
Val Lys Gly Ser Asp Ser Ser Arg Gly Phe Gly Tyr Trp Gly Arg Gly
100 105 110
Ile Leu Val Thr Val Ser Ser
115

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

<220>
<223> Synthetic

<400> 35
gggttcaccc tcagtggaca tggc 24

<210> 36
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 36
Gly Phe Thr Leu Ser Gly His Gly
1 5

<210> 37

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

<220>
<223> Synthetic

<400> 37
atatcatttg atggaggtca tcaa 24

<210> 38
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 38
Ile Ser Phe Asp Gly Gly His Gln
1 5

<210> 39
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 39
gtgaaaggga gcgactcgtc gcgaggtttt ggctac 36

<210> 40
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 40
Val Lys Gly Ser Asp Ser Ser Arg Gly Phe Gly Tyr
1 5 10

<210> 41
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 41
gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtgtttta ttcagttccg acaataagaa ctacttggct 120
tggtaccagc tgaaaccagg tcagcctcct cacctactta tttactgggc atctattcgt 180
gattccgggg tccctgaccg atttagtggc agcgggtctg ggacagattt cacgctcacc 240
atcagcagcc tgcaggctga ggatgtggca gtttactcct gtcatcaata ttatagtgct 300
ccactcacct tcggcggagg gaccaaggtg gagatcaaa 339

<210> 42
<211> 113
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 42
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1   5   10   15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Phe Ser
            20   25   30
Ser Asp Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Leu Lys Pro Gly Gln
        35   40   45
Pro Pro His Leu Leu Ile Tyr Trp Ala Ser Ile Arg Asp Ser Gly Val
    50   55   60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65   70   75   80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Ser Cys His Gln
                85   90   95
Tyr Tyr Ser Ala Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
            100   105   110
Lys

<210> 43
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43
cagagtgttt tattcagttc cgacaataag aactac 36

<210> 44
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 44
Gln Ser Val Leu Phe Ser Ser Asp Asn Lys Asn Tyr
 1   5   10

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

<220>
<223> Synthetic

<400> 45
tgggcatct 9

<210> 46
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46
Trp Ala Ser
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<210> 47
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 47
catcaatatt atagtgctcc actcacc 27

<210> 48
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48
His Gln Tyr Tyr Ser Ala Pro Leu Thr
1 5

<210> 49
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 49
gaggtgcagc tggtggagtc tgggggggac ttggtacaac ctggagggtc cctgagactc 60
tcctgtgcag cctctggagt caccttcagg acatatgaaa tgaattgggt ccgccaggct 120
ccagggaagg gactggagtg gatttcacac attagtagca gtggtgatat tatatactat 180
acaaagtctg tgaagggccg attcaccatc tccagagata acgccaagaa ctcactgttt 240
ctgcaaatga caagtctgag agccgaggac acggctgtat attactgtgc gagagaaagg 300
tacagtcaat acggttatta ttacttcgga atggatgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 50
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 50
Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Thr Phe Arg Thr Tyr
20 25 30
Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Ser His Ile Ser Ser Ser Gly Asp Ile Ile Tyr Tyr Thr Lys Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80
Leu Gln Met Thr Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Arg Tyr Ser Gln Tyr Gly Tyr Tyr Tyr Phe Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 51

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

<220>
<223> Synthetic

<400> 51
ggagtcacct tcaggacata tgaa 24

<210> 52
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 52
Gly Val Thr Phe Arg Thr Tyr Glu
1 5

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

<220>
<223> Synthetic

<400> 53
attagtagca gtggtgatat tata 24

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

<220>
<223> Synthetic

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

<210> 55
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 55
gcgagagaaa ggtacagtca atacggttat tattacttcg gaatggatgt c 51

<210> 56
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56
Ala Arg Glu Arg Tyr Ser Gln Tyr Gly Tyr Tyr Tyr Phe Gly Met Asp
1 5 10 15

Val

<210> 57
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 57
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctataggaga cagagtcacc 60
atcacttgcc gggccagtca gaatactgat aagtggatgg cctggtatca gcagaaagca 120
gggaaagccc ctaaactcct gatctataag gcgtctattt tagaaagtgg ggtcccttca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaagaa tataatactt attttcgggc gttcggccaa 300
gggaccaagg tggaaaccag a 321

<210> 58
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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

<210> 59
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 59
cagaatactg ataagtgg 18

<210> 60
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 60
Gln Asn Thr Asp Lys Trp
 1   5

<210> 61
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 61
aaggcgtct 9

<210> 62
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 62
Lys Ala Ser
1

<210> 63
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 63
caagaatata atacttattt tcgggcg 27

<210> 64
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 64
Gln Glu Tyr Asn Thr Tyr Phe Arg Ala
1 5

<210> 65
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 65
gacgtgcagc tggtggagtc tgggggagac tttgtacaac ctggagggtc cctgagactc 60
tcctgtgcag cctctggagt cgccttcaat gattatgaaa tgaattggat ccgccaggct 120
ccagggaaga gactggagtg gatttcacac attgatagta gtggtactat tatatattac 180
gcagactctg tgaagggccg attcaccatc tccagagaca gcgccaagaa ctcactgttt 240
ctgcaaatgg acagtctgag agccgaggac acggctgttt attactgtgc gagagaaagg 300
tacagtcact acggatatta ctacttcggt atggatgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 66
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 66
Asp Val Gln Leu Val Glu Ser Gly Gly Asp Phe Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Ala Phe Asn Asp Tyr
            20   25   30
Glu Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Ile
        35   40   45
Ser His Ile Asp Ser Ser Gly Thr Ile Ile Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Phe
65   70   75   80
Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Arg Tyr Ser His Tyr Gly Tyr Tyr Tyr Phe Gly Met Asp
            100   105   110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 67
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67
ggagtcgcct tcaatgatta tgaa 24

<210> 68
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 68
Gly Val Ala Phe Asn Asp Tyr Glu
 1   5

<210> 69
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 69
attgatagta gtggtactat tata 24

<210> 70
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 70
Ile Asp Ser Ser Gly Thr Ile Ile
 1   5

<210> 71
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 71
gcgagagaaa ggtacagtca ctacggatat tactacttcg gtatggatgt c 51

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

<220>
<223> Synthetic

<400> 72
Ala Arg Glu Arg Tyr Ser His Tyr Gly Tyr Tyr Tyr Phe Gly Met Asp
1 5 10 15
Val

<210> 73
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 73
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gaatattgat aactggttgg cctggtatca gcagaaaaca 120
ggtaaagccc ctaacctcct gatctataag gcgtctactt tggaaagtgg ggtcccttca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcatcag cctgcagcct 240
gatgattttg caacttatta ctgccaagaa tataatactt attctcggac gttcggccaa 300
ggcaccaagg tggaaatcaa a 321

<210> 74
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 74
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Asp Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45
Tyr Lys Ala Ser Thr Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ile Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Glu Tyr Asn Thr Tyr Ser Arg
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 75
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 75
cagaatattg ataactgg 18

<210> 76
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 76
Gln Asn Ile Asp Asn Trp
1 5

<210> 77
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 77
aaggcgtct 9

<210> 78
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78
Lys Ala Ser
1

<210> 79
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 79
caagaatata atacttattc tcggacg 27

<210> 80
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80
Gln Glu Tyr Asn Thr Tyr Ser Arg Thr

1 5

<210> 81
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 81
gagatacaat tgatagagtc tgggggagac atggtacaac ctggagggtc cctgagactc 60
tcctgtgcag cctctggaat ctcccttaat agttatgaaa tgaattgggt ccgccagact 120
ccagggatgg ggctggagtg gatttcacac ataagtagta gtggaacttc tatatattat 180
gcaaactctg tgaagggccg attcaccata ttcagagaca gcgccaagaa ctcactgttg 240
ctgcaaatga acagtctgag agccgaggac acggctattt attactgtgc aagagaaaga 300
tacgatcact ccgggtatta ctacctcgga atggatgtct ggggcctagg gaccacggtc 360
accgtctcgt ca 372

<210> 82
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 82
Glu Ile Gln Leu Ile Glu Ser Gly Gly Asp Met Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Ser Leu Asn Ser Tyr
20 25 30
Glu Met Asn Trp Val Arg Gln Thr Pro Gly Met Gly Leu Glu Trp Ile
35 40 45
Ser His Ile Ser Ser Ser Gly Thr Ser Ile Tyr Tyr Ala Asn Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Phe Arg Asp Ser Ala Lys Asn Ser Leu Leu
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
Ala Arg Glu Arg Tyr Asp His Ser Gly Tyr Tyr Tyr Leu Gly Met Asp
100 105 110
Val Trp Gly Leu Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 83
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 83
ggaatctccc ttaatagtta tgaa 24

<210> 84
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 84
Gly Ile Ser Leu Asn Ser Tyr Glu
1 5

<210> 85
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 85
ataagtagta gtggaacttc tata 24

<210> 86
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 86
Ile Ser Ser Ser Gly Thr Ser Ile
1 5

<210> 87
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 87
gcaagagaaa gatacgatca ctccgggtat tactacctcg gaatggatgt c 51

<210> 88
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 88
Ala Arg Glu Arg Tyr Asp His Ser Gly Tyr Tyr Tyr Leu Gly Met Asp
1 5 10 15
Val

<210> 89
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 89
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctttaggaga cagagtcacc 60
atcacttgcc gggccagtca gaatattgat aactggatgg cctggtatca gcagaaagtt 120
gggaaagccc ctaaactctt gatatatagg gcgtctactt tagaaactgg ggtcccttca 180
aggttcggcg gcagtggatt tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
ggtgattttg cgacttacta ctgccaagaa tataatagtt attttcggac gttcggccaa 300
gggaccaagg tggagatcaa a 321

<210> 90

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

<220>
<223> Synthetic

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

<210> 91
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 91
cagaatattg ataactgg 18

<210> 92
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 92
Gln Asn Ile Asp Asn Trp
 1   5

<210> 93
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 93
agggcgtct 9

<210> 94
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 94
Arg Ala Ser

1

<210> 95
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 95
caagaatata atagttattt tcggacg 27

<210> 96
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 96
Gln Glu Tyr Asn Ser Tyr Phe Arg Thr
1 5

<210> 97
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 97
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agttacgaca tgcactgggt ccgccaagtt 120
ataggaaaag gtctggagtg ggtctcagct attggtactg ttggtgacac atactatgca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaattc cttgtacctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agatcggggg 300
ggtgcgaata tttatagttt ctactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 98
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 98
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Asp Met His Trp Val Arg Gln Val Ile Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Gly Thr Val Gly Asp Thr Tyr Tyr Ala Gly Ser Val Lys
50 55 60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Asp Arg Gly Gly Ala Asn Ile Tyr Ser Phe Tyr Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 99
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 99
ggattcacct tcagtagtta cgac 24

<210> 100
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 100
Gly Phe Thr Phe Ser Ser Tyr Asp
1 5

<210> 101
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 101
attggtactg ttggtgacac a 21

<210> 102
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 102
Ile Gly Thr Val Gly Asp Thr
1 5

<210> 103
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 103
gcaagagatc gggggggtgc gaatatttat agtttctact acggtatgga cgtc 54

<210> 104
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 104
Ala Arg Asp Arg Gly Gly Ala Asn Ile Tyr Ser Phe Tyr Tyr Gly Met
 1   5   10   15
Asp Val

<210> 105
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 105
gacatccaga tgacccagtc tccatcctcc ctgtctgtat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtca ggacattagc aattatttag cctggtatca gcagaaacca 120
gggaaagttc ctaagctcct gatctatgct gcatccactt tgcaatcagg ggtcccatct 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagatgttg caacttattt ctgtcaaaag tataacagtg ccccattcac tttcggccct 300
gggaccaaag tggatatcaa acga   324

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

<220>
<223> Synthetic

<400> 106
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Val Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Val Ala Thr Tyr Phe Cys Gln Lys Tyr Asn Ser Ala Pro Phe
                85   90   95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
            100   105

<210> 107
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107
caggacatta gcaattat   18

<210> 108
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 108
Gln Asp Ile Ser Asn Tyr

1 5

<210> 109
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 109
gctgcatcc 9

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

<220>
<223> Synthetic

<400> 110
Ala Ala Ser
1

<210> 111
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 111
caaaagtata acagtgcccc attcact 27

<210> 112
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 112
Gln Lys Tyr Asn Ser Ala Pro Phe Thr
1 5

<210> 113
<211> 393
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 113
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttaac agttttgtca tgagctgggt ccgtcaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggtt atggtggtag cacatactac 180
gcagactcca tgaagggccg gttcaccgtc tccagagaca attccaagaa tacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagatcac 300
aaggatttct atgcttcggg gagttatttt aaccgggact actactacgg tatggacgtc 360
tggggccaag ggaccacggt caccgtctcc tca 393

<210> 114

<211> 131
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 114
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Phe
            20   25   30
Val Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ala Ile Ser Gly Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Met
    50   55   60
Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Asp His Lys Asp Phe Tyr Ala Ser Gly Ser Tyr Phe Asn Arg
            100   105   110
Asp Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
        115   120   125
Val Ser Ser
    130

<210> 115
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 115
ggattcacct ttaacagttt tgtc 24

<210> 116
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 116
Gly Phe Thr Phe Asn Ser Phe Val
 1   5

<210> 117
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 117
attagtggtt atggtggtag caca 24

<210> 118
<211> 8
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 118
Ile Ser Gly Tyr Gly Gly Ser Thr
 1   5

<210> 119
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 119
gcgaaagatc acaaggattt ctatgcttcg gggagttatt ttaaccggga ctactactac 60
ggtatggacg tc   72

<210> 120
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 120
Ala Lys Asp His Lys Asp Phe Tyr Ala Ser Gly Ser Tyr Phe Asn Arg
 1   5   10   15
Asp Tyr Tyr Tyr Gly Met Asp Val
            20

<210> 121
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 121
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgttggaga cagagtcacc 60
atcacttgcc gggccagtca gagtattagt agctggttgg cctggtatca gcagaaacca 120
gggaaagccc ctaaggtcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa acga   324

<210> 122
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 122
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
        35   40   45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

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

<210> 123
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 123
cagagtatta gtagctgg 18

<210> 124
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 124
Gln Ser Ile Ser Ser Trp
1 5

<210> 125
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 125
aaggcgtct 9

<210> 126
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 126
Lys Ala Ser
1

<210> 127
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 127
caacagtata atagttattc tcggacg 27

<210> 128
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 128
Gln Gln Tyr Asn Ser Tyr Ser Arg Thr
 1   5

<210> 129
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 129
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgacactc 60
tcctgcgcag cctctagatt caccttcagt aactacgaca tgcactgggt ccgccaagcc 120
acaggaaaag gtctggagtg ggtctcagct attggtactg tcggtgacac atactatgca 180
ggctctgtga agggccgatt caccatctcc agagacgatg ccaagaattc cctttatctc 240
caaatgaaca gcctgagagc cggggacacg gctgtttatt actgtgcaag agatcggggg 300
ggtgcgggga cttatagttt ctattacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca   372

<210> 130
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 130
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Thr Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Asn Tyr
            20   25   30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ala Ile Gly Thr Val Gly Asp Thr Tyr Tyr Ala Gly Ser Val Lys
    50   55   60
Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Ser Leu Tyr Leu
65   70   75   80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95
Arg Asp Arg Gly Gly Ala Gly Thr Tyr Ser Phe Tyr Tyr Gly Met Asp
            100   105   110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 131
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 131
agattcacct tcagtaacta cgac   24

<210> 132
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 132
Arg Phe Thr Phe Ser Asn Tyr Asp
 1   5

<210> 133
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 133
attggtactg tcggtgacac a   21

<210> 134
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 134
Ile Gly Thr Val Gly Asp Thr
 1   5

<210> 135
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 135
gcaagagatc ggggggtgc ggggacttat agtttctatt acggtatgga cgtc   54

<210> 136
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 136
Ala Arg Asp Arg Gly Gly Ala Gly Thr Tyr Ser Phe Tyr Tyr Gly Met
 1   5   10   15
Asp Val

<210> 137
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 137
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtca ggacattagc aattatttag cctggtatca gcagaaacca 120

gggaaagttc ctaaactcct gatctatgct gcttccactt tgcaatcagg ggtcccatct 180
cggttcagtg gtagtggatc tgggacagat ttcactctca ccgtcagcag cctgcagcct 240
gaagatgttg caacttatta ctgtcaaaag tataccagtg ccccattcac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 138
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 138
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Thr Ser Ala Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> 139
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 139
caggacatta gcaattat 18

<210> 140
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 140
Gln Asp Ile Ser Asn Tyr
1 5

<210> 141
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 141
gctgcttcc 9

<210> 142
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 142
Ala Ala Ser
 1

<210> 143
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 143
caaaagtata ccagtgcccc attcact 27

<210> 144
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 144
Gln Lys Tyr Thr Ser Ala Pro Phe Thr
 1   5

<210> 145
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 145
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatgcca tgcactgggt ccgccaggct 120
ccaggcaagg gactggagtg ggtggcaatt atatggtttg atggaagtaa tgaagattat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa catggtatat 240
ctgcaaataa acagcctgag agccgaggac acggctgtgt attactgtgc gagatctgcc 300
aactggaact acgaaggggg acccctcttt gactactggg gccagggaac cctggtcacc 360
gtctcctca 369

<210> 146
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 146
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Ile Ile Trp Phe Asp Gly Ser Asn Glu Asp Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Met Val Tyr
65   70   75   80

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


<210> 147
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 147
ggattcacct tcagtagcta tgcc                                          24

<210> 148
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 148
Gly Phe Thr Phe Ser Ser Tyr Ala
 1               5


<210> 149
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 149
atatggtttg atggaagtaa tgaa                                          24

<210> 150
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 150
Ile Trp Phe Asp Gly Ser Asn Glu
 1               5


<210> 151
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 151
gcgagatctg ccaactggaa ctacgaaggg ggacccctct ttgactac                48

<210> 152
<211> 16
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<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 152
Ala Arg Ser Ala Asn Trp Asn Tyr Glu Gly Gly Pro Leu Phe Asp Tyr
 1   5   10   15

<210> 153
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 153
gacatccaga tgacccagtc tccatcctcc ctgtctgctt ctgtaggaga ccgagtcacc 60
atcacttgcc gggcaagtca gaccattagc acctttttaa attggtatca gcagaagcca 120
gggaaaggcc ctgaactcct gatctacact gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcgctctca ccatcagcag tctgcaacct 240
gaagattttg cgacttacta ctgtcaacag aattacaatg accctcccac cttcggccaa 300
gggacacgac tggagattaa acga   324

<210> 154
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 154
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Thr Phe
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Gly Pro Glu Leu Leu Ile
        35   40   45
Tyr Thr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Ala Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asn Tyr Asn Asp Pro Pro
                85   90   95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
            100   105

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

<220>
<223> Synthetic

<400> 155
cagaccatta gcaccttt   18

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

<220>

<223> Synthetic

<400> 156
Gln Thr Ile Ser Thr Phe
1 5

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

<220>
<223> Synthetic

<400> 157
actgcatcc 9

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

<220>
<223> Synthetic

<400> 158
Thr Ala Ser
1

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

<220>
<223> Synthetic

<400> 159
caacagaatt acaatgaccc tcccacc 27

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

<220>
<223> Synthetic

<400> 160
Gln Gln Asn Tyr Asn Asp Pro Pro Thr
1 5

<210> 161
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 161
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgacactc 60
tcctgtgtag cctctggatt caccttcact gactactaca ttagttggat ccgccaggct 120
ccggggaagg gactggagtg gatttcatac attggtactg gtggtgctgc caaatactac 180
gcagactctg ttaagggccg attcaccgtc tccagggaca acgccaagaa ctcactgtat 240
ctactaatga acaacctgag agccgaggac acggccgtat attattgtgc gagagatctg 300

gggatctttg acttatgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 162
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 162
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Thr Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Thr Asp Tyr
20 25 30
Tyr Ile Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Ser Tyr Ile Gly Thr Gly Gly Ala Ala Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Leu Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Leu Gly Ile Phe Asp Leu Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 163
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 163
ggattcacct tcactgacta ctac 24

<210> 164
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 164
Gly Phe Thr Phe Thr Asp Tyr Tyr
1 5

<210> 165
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 165
attggtactg gtggtgctgc caaa 24

<210> 166
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 166
Ile Gly Thr Gly Gly Ala Ala Lys
 1   5

<210> 167
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 167
gcgagagatc tggggatctt tgactta 27

<210> 168
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 168
Ala Arg Asp Leu Gly Ile Phe Asp Leu
 1   5

<210> 169
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 169
gaaattgtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgta gggccagtca gagtgttagt agtagtttag cctggtacca ccagaaacct 120
ggccaggctc ccaggctcct catccatggt gtttccacca gggccactgg tatcccagcc 180
aggttcagtg gcactgggtc tgggacagaa ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcaacag tatcataact ggcctccgta cactttggc 300
caggggacca agctggagat caaacga 327

<210> 170
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 170
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20   25   30
Leu Ala Trp Tyr His Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
His Gly Val Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Thr Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr His Asn Trp Pro Pro
                85   90   95

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

<210> 171
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 171
cagagtgtta gtagtagt 18

<210> 172
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 172
Gln Ser Val Ser Ser Ser
1 5

<210> 173
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 173
ggtgtttcc 9

<210> 174
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 174
Gly Val Ser
1

<210> 175
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 175
caacagtatc ataactggcc tccgtacact 30

<210> 176
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 176
Gln Gln Tyr His Asn Trp Pro Pro Tyr Thr
 1   5   10

<210> 177
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 177
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agttttggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtgtcaatg atatcaaccg atggaagtaa gaaaaattat 180
gcagactccg tgaagggccg attcaccatc accagagaca attcaaagaa cacgctgtat 240
ttggaaatga acagcctgag agctgaggac acggctgtgt attacggtgt gagagttggg 300
tactatgatt cggggagtta ttataactat tggggccagg gaaccctggt caccgtctcc 360
tca   363

<210> 178
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 178
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
            20   25   30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Met Ile Ser Thr Asp Gly Ser Lys Lys Asn Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Gly
                85   90   95
Val Arg Val Gly Tyr Tyr Asp Ser Gly Ser Tyr Tyr Asn Tyr Trp Gly
            100   105   110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 179
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 179
ggattcacct tcagtagttt tggc   24

<210> 180
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 180
Gly Phe Thr Phe Ser Ser Phe Gly
 1   5

<210> 181
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 181
atatcaaccg atggaagtaa gaaa   24

<210> 182
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 182
Ile Ser Thr Asp Gly Ser Lys Lys
 1   5

<210> 183
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 183
gtgagagttg ggtactatga ttcggggagt tattataact at   42

<210> 184
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 184
Val Arg Val Gly Tyr Tyr Asp Ser Gly Ser Tyr Tyr Asn Tyr
 1   5   10

<210> 185
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 185
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggtga cagagtcacc 60
atcacttgtc gggcgagtca gggtattcgc agctggttag cctggtttca gcagagacca 120
gggaaagccc ctaacctcct gatctatgct gcatccagtt tgcaaagtgg ggtctcatcc 180
aggttcagcg gcagtggctc tgggacagaa ttcactctca gcatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag gcttacagtt ttccgctcac tttcggcgga 300
gggaccaagg tggagatcaa acga   324

<210> 186
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 186
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Ser Trp
            20   25   30
Leu Ala Trp Phe Gln Gln Arg Pro Gly Lys Ala Pro Asn Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Ser Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ser Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Ser Phe Pro Leu
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 187
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 187
cagggtattc gcagctgg 18

<210> 188
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 188
Gln Gly Ile Arg Ser Trp
 1   5

<210> 189
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189
gctgcatcc 9

<210> 190
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 190
Ala Ala Ser
 1

<210> 191
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 191
caacaggctt acagttttcc gctcact 27

<210> 192
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 192
Gln Gln Ala Tyr Ser Phe Pro Leu Thr
 1 5

<210> 193
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 193
gaggtgcagc tggtggagtc tgggggaggc ttggtgcggc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagg atctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaggt attagtggta gtggtgataa tacatactat 180
acagactccg tgaagggccg gttcatcatc tccagagaca attccaagag cacgctgtat 240
ctgcaaatga acagcctgag agccgaagat acggccgtat attactgtgc gagagggtgg 300
gagttactga actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 194
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 194
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Arg Pro Gly Gly
 1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ile Tyr
 20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
Ser Gly Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Thr Asp Ser Val
 50 55 60
Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Ser Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
Ala Arg Gly Trp Glu Leu Leu Asn Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
Thr Val Ser Ser

115

<210> 195
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 195
ggattcacct ttaggatcta tgcc 24

<210> 196
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 196
Gly Phe Thr Phe Arg Ile Tyr Ala
1 5

<210> 197
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 197
attagtggta gtggtgataa taca 24

<210> 198
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 198
Ile Ser Gly Ser Gly Asp Asn Thr
1 5

<210> 199
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 199
gcgagagggt gggagttact gaactac 27

<210> 200
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 200
Ala Arg Gly Trp Glu Leu Leu Asn Tyr
1 5

<210> 201
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 201
gacatccaga tgacccagtc tccatcctca ctgtctgcat ttgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattagc aatcatttag cctggtttca gcagaaacca 120
gggaaagtcc ctaagtccct gatctatgct gcgtccagtt tgcaaagtgg ggtcccatca 180
aaattcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tatggtcttt atcctcccac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 202
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 202
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Phe Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn His
20 25 30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Val Pro Lys Ser Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Gly Leu Tyr Pro Pro
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> 203
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 203
caggacatta gcaatcat 18

<210> 204
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 204
Gln Asp Ile Ser Asn His
1 5

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

<220>
<223> Synthetic

<400> 205
gctgcgtcc 9

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

<220>
<223> Synthetic

<400> 206
Ala Ala Ser
1

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

<220>
<223> Synthetic

<400> 207
caacagtatg gtctttatcc tcccact 27

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

<220>
<223> Synthetic

<400> 208
Gln Gln Tyr Gly Leu Tyr Pro Pro Thr
1 5

<210> 209
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 209
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc cgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacttttagc atctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaggt attagtggta gtggtggtag aacatactac 180
gcagactccg ttaagggccg gttcaccatc tctagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agtcgaggac acggccgttt attactgtgc gagagggtgg 300
gagcttctta acttctgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 210
<211> 116
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 210
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr
            20   25   30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gly Ile Ser Gly Ser Gly Gly Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Gly Trp Glu Leu Leu Asn Phe Trp Gly Gln Gly Thr Leu Val
            100   105   110
Thr Val Ser Ser
        115

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

<220>
<223> Synthetic

<400> 211
ggattcactt ttagcatcta tgcc 24

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

<220>
<223> Synthetic

<400> 212
Gly Phe Thr Phe Ser Ile Tyr Ala
 1   5

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

<220>
<223> Synthetic

<400> 213
attagtggta gtggtggtag aaca 24

<210> 214
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 214
Ile Ser Gly Ser Gly Gly Arg Thr

1 5

<210> 215
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 215
gcgagagggt gggagcttct taacttc 27

<210> 216
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 216
Ala Arg Gly Trp Glu Leu Leu Asn Phe
1 5

<210> 217
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 217
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggcattagt aataatttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcatccagtt tgaaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcaacag cctgcagcct 240
gaagattttg caacttatta ctgccaccag tataatagtt atcctcccac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 218
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 218
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Asn
20 25 30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Lys Ser Gly Val Pro Ser Lys Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Tyr Asn Ser Tyr Pro Pro
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> 219

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

<220>
<223> Synthetic

<400> 219
cagggcatta gtaataat 18

<210> 220
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 220
Gln Gly Ile Ser Asn Asn
1 5

<210> 221
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 221
gctgcatcc 9

<210> 222
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 222
Ala Ala Ser
1

<210> 223
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 223
caccagtata atagttatcc tcccact 27

<210> 224
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 224
His Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 225
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 225
gaggtgcagc tggtggagtc tgggggaggc ttggtgcagc ctgggggtc cctgagactc 60
tcctgtgcag tctctggatt cacctttagc atctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtgataa gacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat tttactgtgc gagagggtgg 300
gagctcctaa actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 226
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 226
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Ser Ile Tyr
            20   25   30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ala Ile Ser Gly Ser Gly Asp Lys Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Phe Tyr Cys
                85   90   95
Ala Arg Gly Trp Glu Leu Leu Asn Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110
Thr Val Ser Ser
        115

<210> 227
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 227
ggattcacct ttagcatcta tgcc 24

<210> 228
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 228
Gly Phe Thr Phe Ser Ile Tyr Ala
 1   5

<210> 229
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 229
attagtggta gtggtgataa gaca 24

<210> 230
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 230
Ile Ser Gly Ser Gly Asp Lys Thr
1 5

<210> 231
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 231
gcgagagggt gggagctcct aaactac 27

<210> 232
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 232
Ala Arg Gly Trp Glu Leu Leu Asn Tyr
1 5

<210> 233
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 233
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtct ggacattagt aatttttag cctggtttca gcagaaacca 120
gggacagccc ctaagtccct gatctattct gcatccagtt tgcggactgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccagcag tatagttctt accctcccac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 234
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 234
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Leu Asp Ile Ser Asn Phe
            20   25   30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Thr Ala Pro Lys Ser Leu Ile
        35   40   45
Tyr Ser Ala Ser Ser Leu Arg Thr Gly Val Pro Ser Lys Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Pro
                85   90   95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
            100   105

<210> 235
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 235
ctggacatta gtaatttt 18

<210> 236
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 236
Leu Asp Ile Ser Asn Phe
 1   5

<210> 237
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 237
tctgcatcc 9

<210> 238
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 238
Ser Ala Ser
 1

<210> 239

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

<220>
<223> Synthetic

<400> 239
cagcagtata gttcttaccc tcccact 27

<210> 240
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 240
Gln Gln Tyr Ser Ser Tyr Pro Pro Thr
1 5

<210> 241
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 241
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ccgggggtc cctgagactc 60
tcctgtgtag cctctggatt caactttaga atctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggccggagtg ggtctcaggt attagtggta gtggtgataa cacatactac 180
gcagcctccg tgaagggccg gttcaccgtc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga ccagcctgag agccgaggac acggccgtat tttactgtgc gagagggtgg 300
gagctcctaa actattgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 242
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 242
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Asn Phe Arg Ile Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
35 40 45
Ser Gly Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Ala Ser Val
50 55 60
Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Thr Ser Leu Arg Ala Glu Asp Thr Ala Val Phe Tyr Cys
85 90 95
Ala Arg Gly Trp Glu Leu Leu Asn Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 243
<211> 24
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 243
ggattcaact ttagaatcta tgcc 24

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

<220>
<223> Synthetic

<400> 244
Gly Phe Asn Phe Arg Ile Tyr Ala
1 5

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

<220>
<223> Synthetic

<400> 245
attagtggta gtggtgataa caca 24

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

<220>
<223> Synthetic

<400> 246
Ile Ser Gly Ser Gly Asp Asn Thr
1 5

<210> 247
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 247
gcgagagggt gggagctcct aaactat 27

<210> 248
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 248
Ala Arg Gly Trp Glu Leu Leu Asn Tyr
1 5

<210> 249
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 249
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtct ggacattggc aatttttag cctggtttca gcagaaacca 120
gggacagccc ctaagtccct gatctattct gcatccagtc tgcagactgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tataattctt atcctcccac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 250
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 250
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Leu Asp Ile Gly Asn Phe
            20   25   30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Thr Ala Pro Lys Ser Leu Ile
        35   40   45
Tyr Ser Ala Ser Ser Leu Gln Thr Gly Val Pro Ser Lys Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
                85   90   95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
            100   105

<210> 251
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 251
ctggacattg gcaatttt 18

<210> 252
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 252
Leu Asp Ile Gly Asn Phe
 1   5

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

<220>
<223> Synthetic

<400> 253
tctgcatcc 9

<210> 254
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 254
Ser Ala Ser
1

<210> 255
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 255
caacagtata attcttatcc tcccact 27

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

<220>
<223> Synthetic

<400> 256
Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 257
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 257
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc cgggggggtc cctgagactc 60
tcctgtgcag cctctggatt tacctttaaa atctatgcca tgagttgggt ccgccagggc 120
ccagggaagg ggctggagtg ggtctcggct attagtggaa atggtgacaa aacatactat 180
acagactccg tgcagggccg gttcaccatc tccagagaca attccaagaa cacactcttt 240
ctccaaatga acagcctgag agccgaggac acggccatat attactgtgc gcgagggtgg 300
gaactgctaa attactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 258
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 258

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

<210> 259
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 259
ggatttacct ttaaaatcta tgcc 24

<210> 260
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 260
Gly Phe Thr Phe Lys Ile Tyr Ala
1 5

<210> 261
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 261
attagtggaa atggtgacaa aaca 24

<210> 262
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 262
Ile Ser Gly Asn Gly Asp Lys Thr
1 5

<210> 263
<211> 27
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 263
gcgcgagggt gggaactgct aaattac 27

<210> 264
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 264
Ala Arg Gly Trp Glu Leu Leu Asn Tyr
1 5

<210> 265
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 265
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctataggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattagc aattctttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatctccag cctgcagcct 240
gaagattttg caacttatta ctgccaacaa tatattcctt tccctcccac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 266
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 266
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Ile Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Ser
20 25 30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Pro Phe Pro Pro
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> 267
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 267
caggacatta gcaattct 18

<210> 268
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 268
Gln Asp Ile Ser Asn Ser
1 5

<210> 269
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 269
gctgcatcc 9

<210> 270
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 270
Ala Ala Ser
1

<210> 271
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 271
caacaatata ttcctttccc tcccact 27

<210> 272
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 272
Gln Gln Tyr Ile Pro Phe Pro Pro Thr
1 5

<210> 273
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 273
gaggtgcagc tggtggagtc tgggggaggc ctggtacagc cgggggggtc cctgagactc 60
tcctgtgtag cttctggatt cacctttacc agctatgcca tgagctgggt ccgccaggct 120
ccagggaggg ggctgcagtg ggtctcagct attggtggta gtggtgatag tatatattac 180
gcagactccg tcaagggccg gttcaccatc tccagagaca actccaagaa tacgctgtat 240
ctgcaaatgg acagcctgag agccgaggac acggccgtat attactgtgc aagaggatgg 300
gagttactca attactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 274
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 274
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Thr Ser Tyr
            20   25   30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Gln Trp Val
        35   40   45
Ser Ala Ile Gly Gly Ser Gly Asp Ser Ile Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Gly Trp Glu Leu Leu Asn Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110
Thr Val Ser Ser
        115

<210> 275
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 275
ggattcacct ttaccagcta tgcc 24

<210> 276
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 276
Gly Phe Thr Phe Thr Ser Tyr Ala
 1   5

<210> 277
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 277
attggtggta gtggtgatag tata 24

<210> 278
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 278
Ile Gly Gly Ser Gly Asp Ser Ile
1 5

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

<220>
<223> Synthetic

<400> 279
gcaagaggat gggagttact caattac 27

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

<220>
<223> Synthetic

<400> 280
Ala Arg Gly Trp Glu Leu Leu Asn Tyr
1 5

<210> 281
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 281
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattggc aatttttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcatccagtt tgaaaagtgg ggtcccatca 180
aagatcagcg gcagtggatc tgggacagat ttcactctca ccatcaacag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tataatattt accctcccac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 282
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 282
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

<210> 283
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 283
caggacattg gcaatttt 18

<210> 284
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 284
Gln Asp Ile Gly Asn Phe
1 5

<210> 285
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 285
gctgcatcc 9

<210> 286
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 286
Ala Ala Ser
1

<210> 287
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 287
caacagtata atatttaccc tcccact 27

<210> 288
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 288
Gln Gln Tyr Asn Ile Tyr Pro Pro Thr
1 5

<210> 289
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 289
caggtacagc tgcagcagtc aggtccagga ctggtgaagc cctcgcagac cctctcactc 60
acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120
cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180
catgattatg ctttttctgt gaaaagtcga atacttatca atccagacac atccaagaac 240
ctgttctccc tgcaagtgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
agagataggc gatcctactt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 290
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 290
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr His Asp Tyr Ala
50 55 60
Phe Ser Val Lys Ser Arg Ile Leu Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80
Leu Phe Ser Leu Gln Val Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95
Tyr Tyr Cys Ala Arg Asp Arg Arg Ser Tyr Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 291
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 291
ggggacagtg tctctagcaa cagtgctgct 30

<210> 292
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 292
Gly Asp Ser Val Ser Ser Asn Ser Ala Ala
1 5 10

<210> 293
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 293
acatactaca ggtccaagtg gtatcat 27

<210> 294
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 294
Thr Tyr Tyr Arg Ser Lys Trp Tyr His
1 5

<210> 295
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 295
gcaagagata ggcgatccta ctttgactac 30

<210> 296
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 296
Ala Arg Asp Arg Arg Ser Tyr Phe Asp Tyr
1 5 10

<210> 297
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 297
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtcg gagtgttagc agttccttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtg gcggtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcagcag cgtaacaact ggcctcccac ttttggccag 300
gggaccaagc tggagatcaa acga 324

<210> 298
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 298
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Arg Ser Val Ser Ser Ser
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Pro
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 299
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 299
cggagtgtta gcagttcc 18

<210> 300
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 300
Arg Ser Val Ser Ser Ser
1 5

<210> 301
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 301

gatgcatcc 9

<210> 302
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 302
Asp Ala Ser
1

<210> 303
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 303
cagcagcgta acaactggcc tcccact 27

<210> 304
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 304
Gln Gln Arg Asn Asn Trp Pro Pro Thr
1 5

<210> 305
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 305
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtacag cctctggatt cgtttttgaa gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
acggactctg tgaagggccg attcaccgtc tccagagaca acgccaagaa ctccttgtat 240
ctgcaaatga acagtctgac aactgaggac acggccttgt attattgtgc aaaagataaa 300
tcgccctcta agtggaactt actaggtatg gacgtctggg gccaagggac cacggtcacc 360
gtctcctca 369

<210> 306
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 306
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Val Phe Glu Asp Tyr
20 25 30

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

<210> 307
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 307
ggattcgttt ttgaagatta tgcc 24

<210> 308
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 308
Gly Phe Val Phe Glu Asp Tyr Ala
1 5

<210> 309
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 309
attagttgga atagtggtag gata 24

<210> 310
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 310
Ile Ser Trp Asn Ser Gly Arg Ile
1 5

<210> 311
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 311
gcaaaagata aatcgccctc taagtggaac ttactaggta tggacgtc 48

<210> 312
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 312
Ala Lys Asp Lys Ser Pro Ser Lys Trp Asn Leu Leu Gly Met Asp Val
1 5 10 15

<210> 313
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 313
gccatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggacattaga aatgatttag gctggtttca gcagaaacca 120
gggagagccc ctaacctcct aatctttggt gcatccagtt tacaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcgg cctgcagcct 240
gaagattttt caacttatta ctgtctacaa gattacactt acccattcac tttcggccct 300
gggaccaaag tggatatcaa acga 324

<210> 314
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 314
Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
20 25 30
Leu Gly Trp Phe Gln Gln Lys Pro Gly Arg Ala Pro Asn Leu Leu Ile
35 40 45
Phe Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu Gln Pro
65 70 75 80
Glu Asp Phe Ser Thr Tyr Tyr Cys Leu Gln Asp Tyr Thr Tyr Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> 315
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 315
caggacatta gaaatgat 18

<210> 316
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 316
Gln Asp Ile Arg Asn Asp
 1   5

<210> 317
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 317
ggtgcatcc   9

<210> 318
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 318
Gly Ala Ser
 1

<210> 319
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 319
ctacaagatt acacttaccc attcact   27

<210> 320
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 320
Leu Gln Asp Tyr Thr Tyr Pro Phe Thr
 1   5

<210> 321
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 321
caggtgcagc tggtgcagtc tggggctgag gtacagaagc ccggggcgtc agtgaaagtc 60
tcctgcaagg cttctggata caccttcacc gactactata ttcattgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcaacccta aaactggtgg cacaaactat 180
gcaccgaagt ttcagggcag ggtcaccatg accagggact cgtccatcat cacagcctac 240
atggacttga ccagactgac ctctgacgac acggccgtgt tttactgtgc gagacgggga 300
tataatagta ggtggtccgt ttttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

<210> 322
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 322
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Gln Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Asn Pro Lys Thr Gly Gly Thr Asn Tyr Ala Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Ser Ser Ile Ile Thr Ala Tyr
65 70 75 80
Met Asp Leu Thr Arg Leu Thr Ser Asp Asp Thr Ala Val Phe Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Asn Ser Arg Trp Ser Val Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 323
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 323
ggatacacct tcaccgacta ctat 24

<210> 324
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 324
Gly Tyr Thr Phe Thr Asp Tyr Tyr
1 5

<210> 325
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 325

atcaacccta aaactggtgg caca 24

<210> 326
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 326
Ile Asn Pro Lys Thr Gly Gly Thr
1 5

<210> 327
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 327
gcgagacggg gatataatag taggtggtcc gtttttgact ac 42

<210> 328
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 328
Ala Arg Arg Gly Tyr Asn Ser Arg Trp Ser Val Phe Asp Tyr
1 5 10

<210> 329
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 329
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgta gggccagtca gagtgtttac agcaactact tagcctggta ccagcagaaa 120
cgtggcctgg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagcatggtg gctcaccggt cactttcggc 300
ggagggacca aggtggagat caaacga 327

<210> 330
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 330
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Ser Asn
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Arg Gly Leu Ala Pro Arg Leu Leu

```
        35                  40                  45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Gly Gly Ser Pro
                85                  90                  95
Val Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100                 105
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<210> 331
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 331
cagagtgttt acagcaacta c 21

<210> 332
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 332
Gln Ser Val Tyr Ser Asn Tyr
 1   5

<210> 333
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 333
ggtgcatcc 9

<210> 334
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 334
Gly Ala Ser
 1

<210> 335
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 335
cagcagcatg gtggctcacc ggtcact 27

<210> 336
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 336
Gln Gln His Gly Gly Ser Pro Val Thr
 1   5

<210> 337
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 337
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgaag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaacg ggctggagtg gatcgcagtt atatcatctg atggaaataa taaatattat 180
atagaatccg tgaagggccg attcaccatg tccagagaca attccaagaa cacgctgtat 240
ctgcaattga acagcctgag aactgaggac acggctgtgt attactgtgc gacttacaac 300
tggaacgacg acggggacgg ggtttttgac tactggggcc agggaaccct ggtcaccgtc 360
tcctca   366

<210> 338
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 338
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Gly Met His Trp Val Arg Gln Ala Pro Gly Asn Gly Leu Glu Trp Ile
        35   40   45
Ala Val Ile Ser Ser Asp Gly Asn Asn Lys Tyr Tyr Ile Glu Ser Val
    50   55   60
Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Leu Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Thr Tyr Asn Trp Asn Asp Asp Gly Asp Gly Val Phe Asp Tyr Trp
            100   105   110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

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

<220>
<223> Synthetic

<400> 339
ggattcacct tcagtagcta tggc   24

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

<220>
<223> Synthetic

<400> 340
Gly Phe Thr Phe Ser Ser Tyr Gly
 1   5

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

<220>
<223> Synthetic

<400> 341
atatcatctg atggaaataa taaa   24

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

<220>
<223> Synthetic

<400> 342
Ile Ser Ser Asp Gly Asn Asn Lys
 1   5

<210> 343
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 343
gcgacttaca actggaacga cgacggggac ggggtttttg actac   45

<210> 344
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 344
Ala Thr Tyr Asn Trp Asn Asp Asp Gly Asp Gly Val Phe Asp Tyr
 1   5   10   15

<210> 345
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 345
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc aactggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatggt acatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag gttaagagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa acga 324

<210> 346
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 346
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Gly Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Lys Ser Phe Pro Tyr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

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

<220>
<223> Synthetic

<400> 347
cagggtatta gcaactgg 18

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

<220>
<223> Synthetic

<400> 348
Gln Gly Ile Ser Asn Trp
1 5

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

<220>
<223> Synthetic

<400> 349
ggtacatcc 9

<210> 350

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

<220>
<223> Synthetic

<400> 350
Gly Thr Ser
 1

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

<220>
<223> Synthetic

<400> 351
caacaggtta agagtttccc gtacact 27

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

<220>
<223> Synthetic

<400> 352
Gln Gln Val Lys Ser Phe Pro Tyr Thr
 1   5

<210> 353
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 353
gaggtgcagc tggtggagtc ggggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agatatggca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacataccac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacactgtat 240
ctgcaaatga atagcctgag agccgcggac acggccatat atttctgtgc gtcttacaat 300
tggaacgacg gggtggacgt ctggggccaa gggaccacgg tcaccgtctc ctca 354

<210> 354
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 354
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20   25   30
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr His Ala Asp Ser Val
    50   55   60

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

<210> 355
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 355
ggattcacct ttagcagata tggc 24

<210> 356
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 356
Gly Phe Thr Phe Ser Arg Tyr Gly
1 5

<210> 357
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 357
attagtggta gtggtggtag caca 24

<210> 358
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 358
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 359
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 359
gcgtcttaca attggaacga cggggtggac gtc 33

<210> 360
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 360
Ala Ser Tyr Asn Trp Asn Asp Gly Val Asp Val
 1   5   10

<210> 361
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 361
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctataggaga cagggtcacc 60
atcacttgtc gggcgagtca gggtattagc aactggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatggt gcatccagtt tgcaaagtgg agtctcatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcatcag ccttcagcct 240
gaagattttg caacttacta ttgtcaacag gctaacagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa acga   324

<210> 362
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 362
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Ile Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Ser Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ile Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            100   105

<210> 363
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 363
cagggtatta gcaactgg   18

<210> 364
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 364
Gln Gly Ile Ser Asn Trp
 1   5

<210> 365
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 365
ggtgcatcc   9

<210> 366
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 366
Gly Ala Ser
 1

<210> 367
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 367
caacaggcta acagtttccc gtacact   27

<210> 368
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 368
Gln Gln Ala Asn Ser Phe Pro Tyr Thr
 1   5

<210> 369
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 369
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp

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            20                  25                  30
Leu Ala Trp Tyr Gln His Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Trp
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205
Phe Asn Arg Gly Glu Cys
    210


<210> 370
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 370
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asn Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Leu Ile Trp Tyr Asp Gly Ser Asn Glu Asp Tyr Thr Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Met Val Arg Gly Val Ile Asp Val Phe Asp Ile Trp
            100                 105                 110
Gly Gln Gly Thr Val Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220
Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
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            260                 265                 270
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445
Ser Pro Gly Lys
    450
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<210> 371
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 371

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Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Thr
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205
Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 372
<211> 449
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 372
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Ser 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
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45
Gly Ile Phe Tyr Pro Gly Asp Ser Ser Thr Arg Tyr Ser Pro Ser Phe
    50   55   60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Val Asn 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 Arg Arg Asn Trp Gly Asn Ala Phe Asp Ile Trp Gly Gln Gly
            100   105   110
Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115   120   125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130   135   140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145   150   155   160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165   170   175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180   185   190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195   200   205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210   215   220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225   230   235   240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245   250   255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260   265   270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275   280   285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290   295   300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305   310   315   320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325   330   335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340   345   350
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355   360   365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370   375   380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385   390   395   400
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405   410   415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420   425   430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435   440   445
Lys

<210> 373
<211> 213
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 373
Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
 1   5   10   15
Glu Arg Val Thr Phe Asn Cys Arg Ala Ser Glu Asn Val Gly Thr Tyr
            20   25   30
Val Phe Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro Arg Leu Leu Ile
        35   40   45
Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60
Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Gly Val Gln Ala
65   70   75   80
Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Ser Tyr Arg His Leu Thr
                85   90   95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala Pro
            100   105   110
Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
        115   120   125
Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
    130   135   140
Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145   150   155   160
Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165   170   175
Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180   185   190
Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195   200   205
Asn Arg Gly Glu Cys
    210

<210> 374
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 374
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1   5   10   15
Ser Val Arg Leu Ser Cys Lys Ala Gly Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30
Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Met Ile His Pro Asn Ser Gly Ser Tyr Asp Tyr Ser Glu Thr Phe
    50   55   60
Arg Thr Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asp Thr Ala Tyr
65   70   75   80
Met Gln Leu Thr Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Gly Gly Ser Asn Tyr Asp Ile Phe Ala Tyr Trp Gly Gln Gly
            100   105   110
Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115   120   125
Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
    130   135   140
Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145   150   155   160
Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165   170   175
Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180   185   190

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Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205
Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys
    210                 215                 220
Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro
225                 230                 235                 240
Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
                245                 250                 255
Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
            260                 265                 270
Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
        275                 280                 285
Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
    290                 295                 300
Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
305                 310                 315                 320
Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg
                325                 330                 335
Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val
            340                 345                 350
Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr
        355                 360                 365
Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
    370                 375                 380
Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu
385                 390                 395                 400
Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys
                405                 410                 415
Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
            420                 425                 430
Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
        435                 440                 445
Lys
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<210> 375
<211> 863
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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<400> 375
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Phe Asp Ile Asn Thr Gly Ala Ala Leu Ile Ser Tyr Lys Ile Ile Asn
            20                  25                  30
Gly Lys His Phe Tyr Phe Asn Asn Asp Gly Val Met Gln Leu Gly Val
        35                  40                  45
Phe Lys Gly Pro Asp Gly Phe Glu Tyr Phe Ala Pro Ala Asn Thr Gln
    50                  55                  60
Asn Asn Asn Ile Glu Gly Gln Ala Ile Val Tyr Gln Ser Lys Phe Leu
65                  70                  75                  80
Thr Leu Asn Gly Lys Lys Tyr Tyr Phe Asp Asn Asp Ser Lys Ala Val
                85                  90                  95
Thr Gly Trp Arg Ile Ile Asn Asn Glu Lys Tyr Tyr Phe Asn Pro Asn
            100                 105                 110
Asn Ala Ile Ala Ala Val Gly Leu Gln Val Ile Asp Asn Asn Lys Tyr
        115                 120                 125
Tyr Phe Asn Pro Asp Thr Ala Ile Ile Ser Lys Gly Trp Gln Thr Val
    130                 135                 140
Asn Gly Ser Arg Tyr Tyr Phe Asp Thr Asp Thr Ala Ile Ala Phe Asn
145                 150                 155                 160
Gly Tyr Lys Thr Ile Asp Gly Lys His Phe Tyr Phe Asp Ser Asp Cys
                165                 170                 175
Val Val Lys Ile Gly Val Phe Ser Thr Ser Asn Gly Phe Glu Tyr Phe
            180                 185                 190
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Ala Pro Ala Asn Thr Tyr Asn Asn Asn Ile Glu Gly Gln Ala Ile Val
        195                 200                 205
Tyr Gln Ser Lys Phe Leu Thr Leu Asn Gly Lys Lys Tyr Tyr Phe Asp
    210                 215                 220
Asn Asn Ser Lys Ala Val Thr Gly Trp Gln Thr Ile Asp Ser Lys Lys
225                 230                 235                 240
Tyr Tyr Phe Asn Thr Asn Thr Ala Glu Ala Ala Thr Gly Trp Gln Thr
                245                 250                 255
Ile Asp Gly Lys Lys Tyr Tyr Phe Asn Thr Asn Thr Ala Glu Ala Ala
            260                 265                 270
Thr Gly Trp Gln Thr Ile Asp Gly Lys Lys Tyr Tyr Phe Asn Thr Asn
        275                 280                 285
Thr Ala Ile Ala Ser Thr Gly Tyr Thr Ile Ile Asn Gly Lys His Phe
    290                 295                 300
Tyr Phe Asn Thr Asp Gly Ile Met Gln Ile Gly Val Phe Lys Gly Pro
305                 310                 315                 320
Asn Gly Phe Glu Tyr Phe Ala Pro Ala Asn Thr Asp Ala Asn Asn Ile
                325                 330                 335
Glu Gly Gln Ala Ile Leu Tyr Gln Asn Glu Phe Leu Thr Leu Asn Gly
            340                 345                 350
Lys Lys Tyr Tyr Phe Gly Ser Asp Ser Lys Ala Val Thr Gly Trp Arg
        355                 360                 365
Ile Ile Asn Asn Lys Lys Tyr Tyr Phe Asn Pro Asn Asn Ala Ile Ala
    370                 375                 380
Ala Ile His Leu Cys Thr Ile Asn Asn Asp Lys Tyr Tyr Phe Ser Tyr
385                 390                 395                 400
Asp Gly Ile Leu Gln Asn Gly Tyr Ile Thr Ile Glu Arg Asn Asn Phe
                405                 410                 415
Tyr Phe Asp Ala Asn Asn Glu Ser Lys Met Val Thr Gly Val Phe Lys
            420                 425                 430
Gly Pro Asn Gly Phe Glu Tyr Phe Ala Pro Ala Asn Thr His Asn Asn
        435                 440                 445
Asn Ile Glu Gly Gln Ala Ile Val Tyr Gln Asn Lys Phe Leu Thr Leu
    450                 455                 460
Asn Gly Lys Lys Tyr Tyr Phe Asp Asn Asp Ser Lys Ala Val Thr Gly
465                 470                 475                 480
Trp Gln Thr Ile Asp Gly Lys Lys Tyr Tyr Phe Asn Leu Asn Thr Ala
                485                 490                 495
Glu Ala Ala Thr Gly Trp Gln Thr Ile Asp Gly Lys Lys Tyr Tyr Phe
            500                 505                 510
Asn Leu Asn Thr Ala Glu Ala Ala Thr Gly Trp Gln Thr Ile Asp Gly
        515                 520                 525
Lys Lys Tyr Tyr Phe Asn Thr Asn Thr Phe Ile Ala Ser Thr Gly Tyr
    530                 535                 540
Thr Ser Ile Asn Gly Lys His Phe Tyr Phe Asn Thr Asp Gly Ile Met
545                 550                 555                 560
Gln Ile Gly Val Phe Lys Gly Pro Asn Gly Phe Glu Tyr Phe Ala Pro
                565                 570                 575
Ala Asn Thr His Asn Asn Asn Ile Glu Gly Gln Ala Ile Leu Tyr Gln
            580                 585                 590
Asn Lys Phe Leu Thr Leu Asn Gly Lys Lys Tyr Tyr Phe Gly Ser Asp
        595                 600                 605
Ser Lys Ala Val Thr Gly Leu Arg Thr Ile Asp Gly Lys Lys Tyr Tyr
    610                 615                 620
Phe Asn Thr Asn Thr Ala Val Ala Val Thr Gly Trp Gln Thr Ile Asn
625                 630                 635                 640
Gly Lys Lys Tyr Tyr Phe Asn Thr Asn Thr Ser Ile Ala Ser Thr Gly
                645                 650                 655
Tyr Thr Ile Ile Ser Gly Lys His Phe Tyr Phe Asn Thr Asp Gly Ile
            660                 665                 670
Met Gln Ile Gly Val Phe Lys Gly Pro Asp Gly Phe Glu Tyr Phe Ala
        675                 680                 685
Pro Ala Asn Thr Asp Ala Asn Asn Ile Glu Gly Gln Ala Ile Arg Tyr
    690                 695                 700
Gln Asn Arg Phe Leu Tyr Leu His Asp Asn Ile Tyr Tyr Phe Gly Asn
705                 710                 715                 720
Asn Ser Lys Ala Ala Thr Gly Trp Val Thr Ile Asp Gly Asn Arg Tyr
                725                 730                 735
Tyr Phe Glu Pro Asn Thr Ala Met Gly Ala Asn Gly Tyr Lys Thr Ile
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            740                 745                 750
Asp Asn Lys Asn Phe Tyr Phe Arg Asn Gly Leu Pro Gln Ile Gly Val
        755                 760                 765
Phe Lys Gly Ser Asn Gly Phe Glu Tyr Phe Ala Pro Ala Asn Thr Asp
    770                 775                 780
Ala Asn Asn Ile Glu Gly Gln Ala Ile Arg Tyr Gln Asn Arg Phe Leu
785                 790                 795                 800
His Leu Leu Gly Lys Ile Tyr Tyr Phe Gly Asn Asn Ser Lys Ala Val
                805                 810                 815
Thr Gly Trp Gln Thr Ile Asn Gly Lys Val Tyr Tyr Phe Met Pro Asp
            820                 825                 830
Thr Ala Met Ala Ala Ala Gly Gly Leu Phe Glu Ile Asp Gly Val Ile
        835                 840                 845
Tyr Phe Phe Gly Val Asp Gly Val Lys Ala Pro Gly Ile Tyr Gly
    850                 855                 860


<210> 376
<211> 516
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 376
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Asn Pro Ile Asn Gly Gly Ala Ala Ser Ile Gly Glu Thr Ile Ile Asp
            20                  25                  30
Asp Lys Asn Tyr Tyr Phe Asn Gln Ser Gly Val Leu Gln Thr Gly Val
        35                  40                  45
Phe Ser Thr Glu Asp Gly Phe Lys Tyr Phe Ala Pro Ala Asn Thr Leu
    50                  55                  60
Asp Glu Asn Leu Glu Gly Glu Ala Ile Asp Phe Thr Gly Lys Leu Ile
65                  70                  75                  80
Ile Asp Glu Asn Ile Tyr Tyr Phe Asp Asp Asn Tyr Arg Gly Ala Val
                85                  90                  95
Glu Trp Lys Glu Leu Asp Gly Glu Met His Tyr Phe Ser Pro Glu Thr
            100                 105                 110
Gly Lys Ala Phe Lys Gly Leu Asn Gln Ile Gly Asp Tyr Lys Tyr Tyr
        115                 120                 125
Phe Asn Ser Asp Gly Val Met Gln Lys Gly Phe Val Ser Ile Asn Asp
    130                 135                 140
Asn Lys His Tyr Phe Asp Asp Ser Gly Val Met Lys Val Gly Tyr Thr
145                 150                 155                 160
Glu Ile Asp Gly Lys His Phe Tyr Phe Ala Glu Asn Gly Glu Met Gln
                165                 170                 175
Ile Gly Val Phe Asn Thr Glu Asp Gly Phe Lys Tyr Phe Ala His His
            180                 185                 190
Asn Glu Asp Leu Gly Asn Glu Glu Gly Glu Glu Ile Ser Tyr Ser Gly
        195                 200                 205
Ile Leu Asn Phe Asn Asn Lys Ile Tyr Tyr Phe Asp Asp Ser Phe Thr
    210                 215                 220
Ala Val Val Gly Trp Lys Asp Leu Glu Asp Gly Ser Lys Tyr Tyr Phe
225                 230                 235                 240
Asp Glu Asp Thr Ala Glu Ala Tyr Ile Gly Leu Ser Leu Ile Asn Asp
                245                 250                 255
Gly Gln Tyr Tyr Phe Asn Asp Asp Gly Ile Met Gln Val Gly Phe Val
            260                 265                 270
Thr Ile Asn Asp Lys Val Phe Tyr Phe Ser Asp Ser Gly Ile Ile Glu
        275                 280                 285
Ser Gly Val Gln Asn Ile Asp Asp Asn Tyr Phe Tyr Ile Asp Asp Asn
    290                 295                 300
Gly Ile Val Gln Ile Gly Val Phe Asp Thr Ser Asp Gly Tyr Lys Tyr
305                 310                 315                 320
Phe Ala Pro Ala Asn Thr Val Asn Asp Asn Ile Tyr Gly Gln Ala Val
                325                 330                 335
Glu Tyr Ser Gly Leu Val Arg Val Gly Glu Asp Val Tyr Tyr Phe Gly
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            340                 345                 350
Glu Thr Tyr Thr Ile Glu Thr Gly Trp Ile Tyr Asp Met Glu Asn Glu
        355                 360                 365
Ser Asp Lys Tyr Tyr Phe Asn Pro Glu Thr Lys Lys Ala Cys Lys Gly
    370                 375                 380
Ile Asn Leu Ile Asp Asp Ile Lys Tyr Tyr Phe Asp Glu Lys Gly Ile
385                 390                 395                 400
Met Arg Thr Gly Leu Ile Ser Phe Glu Asn Asn Asn Tyr Tyr Phe Asn
                405                 410                 415
Glu Asn Gly Glu Met Gln Phe Gly Tyr Ile Asn Ile Glu Asp Lys Met
            420                 425                 430
Phe Tyr Phe Gly Glu Asp Gly Val Met Gln Ile Gly Val Phe Asn Thr
        435                 440                 445
Pro Asp Gly Phe Lys Tyr Phe Ala His Gln Asn Thr Leu Asp Glu Asn
    450                 455                 460
Phe Glu Gly Glu Ser Ile Asn Tyr Thr Gly Trp Leu Asp Leu Asp Glu
465                 470                 475                 480
Lys Arg Tyr Tyr Phe Thr Asp Glu Tyr Ile Ala Ala Thr Gly Ser Val
                485                 490                 495
Ile Ile Asp Gly Glu Glu Tyr Tyr Phe Asp Pro Asp Thr Ala Gln Leu
            500                 505                 510
Val Ile Ser Glu
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<210> 377
<211> 8133
<212> DNA
<213> Clostridium difficile

<400> 377

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<212> PRT
<213> Clostridium difficile

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Tyr Asn Lys Leu Thr Thr Asn Asn Asn Glu Asn Lys Tyr Leu Gln Leu
        35                  40                  45
Lys Lys Leu Asn Glu Ser Ile Asp Val Phe Met Asn Lys Tyr Lys Thr
    50                  55                  60
Ser Ser Arg Asn Arg Ala Leu Ser Asn Leu Lys Lys Asp Ile Leu Lys
65                  70                  75                  80
Glu Val Ile Leu Ile Lys Asn Ser Asn Thr Ser Pro Val Glu Lys Asn
                85                  90                  95
Leu His Phe Val Trp Ile Gly Gly Glu Val Ser Asp Ile Ala Leu Glu
            100                 105                 110
Tyr Ile Lys Gln Trp Ala Asp Ile Asn Ala Glu Tyr Asn Ile Lys Leu
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Trp Tyr Asp Ser Glu Ala Phe Leu Val Asn Thr Leu Lys Lys Ala Ile
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Val Glu Ser Ser Thr Thr Glu Ala Leu Gln Leu Leu Glu Glu Glu Ile
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Gln Asn Pro Gln Phe Asp Asn Met Lys Phe Tyr Lys Lys Arg Met Glu
                165                 170                 175
Phe Ile Tyr Asp Arg Gln Lys Arg Phe Ile Asn Tyr Tyr Lys Ser Gln
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Ile Asn Lys Pro Thr Val Pro Thr Ile Asp Asp Ile Ile Lys Ser His
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Leu Val Ser Glu Tyr Asn Arg Asp Glu Thr Val Leu Glu Ser Tyr Arg
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Thr Asn Ser Leu Arg Lys Ile Asn Ser Asn His Gly Ile Asp Ile Arg
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Ala Asn Ser Leu Phe Thr Glu Gln Glu Leu Leu Asn Ile Tyr Ser Gln
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Glu Leu Leu Asn Arg Gly Asn Leu Ala Ala Ala Ser Asp Ile Val Arg
            260                 265                 270
Leu Leu Ala Leu Lys Asn Phe Gly Gly Val Tyr Leu Asp Val Asp Met
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Leu Pro Gly Ile His Ser Asp Leu Phe Lys Thr Ile Ser Arg Pro Ser
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Ser Ile Gly Leu Asp Arg Trp Glu Met Ile Lys Leu Glu Ala Ile Met
305                 310                 315                 320
Lys Tyr Lys Lys Tyr Ile Asn Asn Tyr Thr Ser Glu Asn Phe Asp Lys
                325                 330                 335
Leu Asp Gln Gln Leu Lys Asp Asn Phe Lys Leu Ile Ile Glu Ser Lys
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Ser Glu Lys Ser Glu Ile Phe Ser Lys Leu Glu Asn Leu Asn Val Ser
        355                 360                 365
Asp Leu Glu Ile Lys Ile Ala Phe Ala Leu Gly Ser Val Ile Asn Gln
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Ala Leu Ile Ser Lys Gln Gly Ser Tyr Leu Thr Asn Leu Val Ile Glu
385                 390                 395                 400
Gln Val Lys Asn Arg Tyr Gln Phe Leu Asn Gln His Leu Asn Pro Ala
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Ile Glu Ser Asp Asn Asn Phe Thr Asp Thr Thr Lys Ile Phe His Asp
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Ser Leu Phe Asn Ser Ala Thr Ala Glu Asn Ser Met Phe Leu Thr Lys
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Ile Ala Pro Tyr Leu Gln Val Gly Phe Met Pro Glu Ala Arg Ser Thr
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Asp Asn Gly Val Asp Phe Asn Lys Asn Thr Ala Leu Asp Lys Asn Tyr
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Leu Leu Asn Asn Lys Ile Pro Ser Asn Asn Val Glu Glu Ala Gly Ser
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Lys Asn Tyr Val His Tyr Ile Ile Gln Leu Gln Gly Asp Asp Ile Ser
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Tyr Glu Ala Thr Cys Asn Leu Phe Ser Lys Asn Pro Lys Asn Ser Ile
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Ile Ile Gln Arg Asn Met Asn Glu Ser Ala Lys Ser Tyr Phe Leu Ser
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Asp Asp Gly Glu Ser Ile Leu Glu Leu Asn Lys Tyr Arg Ile Pro Glu
625                 630                 635                 640
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Lys Asp Glu Phe Asn Thr Ser Glu Phe Ala Arg Leu Ser Val Asp Ser
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Leu Ser Asn Glu Ile Ser Ser Phe Leu Asp Thr Ile Lys Leu Asp Ile
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Ser Pro Lys Asn Val Glu Val Asn Leu Leu Gly Cys Asn Met Phe Ser
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Tyr Asp Phe Asn Val Glu Glu Thr Tyr Pro Gly Lys Leu Leu Leu Ser
705                 710                 715                 720
Ile Met Asp Lys Ile Thr Ser Thr Leu Pro Asp Val Asn Lys Asn Ser
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Ile Thr Ile Gly Ala Asn Gln Tyr Glu Val Arg Ile Asn Ser Glu Gly
            740                 745                 750
Arg Lys Glu Leu Leu Ala His Ser Gly Lys Trp Ile Asn Lys Glu Glu
        755                 760                 765
Ala Ile Met Ser Asp Leu Ser Ser Lys Glu Tyr Ile Phe Phe Asp Ser
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Ile Asp Asn Lys Leu Lys Ala Lys Ser Lys Asn Ile Pro Gly Leu Ala
785                 790                 795                 800
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Pro Asp Thr Lys Phe Ile Leu Asn Asn Leu Lys Leu Asn Ile Glu Ser
            820                 825                 830
Ser Ile Gly Asp Tyr Ile Tyr Tyr Glu Lys Leu Glu Pro Val Lys Asn
        835                 840                 845
Ile Ile His Asn Ser Ile Asp Asp Leu Ile Asp Glu Phe Asn Leu Leu
    850                 855                 860
Glu Asn Val Ser Asp Glu Leu Tyr Glu Leu Lys Lys Leu Asn Asn Leu
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Asp Glu Lys Tyr Leu Ile Ser Phe Glu Asp Ile Ser Lys Asn Asn Ser
                885                 890                 895
Thr Tyr Ser Val Arg Phe Ile Asn Lys Ser Asn Gly Glu Ser Val Tyr
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Val Glu Thr Glu Lys Glu Ile Phe Ser Lys Tyr Ser Glu His Ile Thr
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Lys Glu Ile Ser Thr Ile Lys Asn Ser Ile Ile Thr Asp Val Asn Gly
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Asn Leu Leu Asp Asn Ile Gln Leu Asp His Thr Ser Gln Val Asn Thr
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Lys Asp Val Leu Asn Asp Leu Ser Thr Ser Val Lys Val Gln Leu Tyr
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Ala Glu Val Thr Ile Phe Leu Leu Pro Ile Ala Gly Ile Ser Ala Gly
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Ser Val Val Asn Tyr Phe Asn His Leu Ser Glu Ser Lys Lys Tyr Gly
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Pro Leu Lys Thr Glu Asp Asp Lys Ile Leu Val Pro Ile Asp Asp Leu
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Val Ile Ser Glu Ile Asp Phe Asn Asn Asn Ser Ile Lys Leu Gly Thr
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Cys Asn Ile Leu Ala Met Glu Gly Gly Ser Gly His Thr Val Thr Gly
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Asn Ile Asp His Phe Phe Ser Ser Pro Ser Ile Ser Ser His Ile Pro
1185                1190                1195                1200
Ser Leu Ser Ile Tyr Ser Ala Ile Gly Ile Glu Thr Glu Asn Leu Asp
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Phe Ser Lys Lys Ile Met Met Leu Pro Asn Ala Pro Ser Arg Val Phe
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Trp Trp Glu Thr Gly Ala Val Pro Gly Leu Arg Ser Leu Glu Asn Asp
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Gly Thr Arg Leu Leu Asp Ser Ile Arg Asp Leu Tyr Pro Gly Lys Phe
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Tyr Trp Arg Phe Tyr Ala Phe Phe Asp Tyr Ala Ile Thr Thr Leu Lys
1265                1270                1275                1280
Pro Val Tyr Glu Asp Thr Asn Ile Lys Ile Lys Leu Asp Lys Asp Thr
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Arg Asn Phe Ile Met Pro Thr Ile Thr Thr Asn Glu Ile Arg Asn Lys
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Leu Ser Tyr Ser Phe Asp Gly Ala Gly Gly Thr Tyr Ser Leu Leu Leu
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Ser Ser Tyr Pro Ile Ser Thr Asn Ile Asn Leu Ser Lys Asp Asp Leu
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Trp Ile Phe Asn Ile Asp Asn Glu Val Arg Glu Ile Ser Ile Glu Asn
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1380 1385 1390
Ser Gly Asp Ile Asp Asn Lys Asp Arg Tyr Ile Phe Leu Thr Cys Glu
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Leu Ser Asn Thr Ile Glu Lys Ile Asn Thr Leu Gly Leu Asp Ser Lys
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1475 1480 1485
Ser Lys Asn Ile Leu Glu Phe Tyr Asn Asp Ser Thr Leu Glu Phe Asn
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Ser Lys Asp Phe Ile Ala Glu Asp Ile Asn Val Phe Met Lys Asp Asp
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Ser Ile Asp Phe Ser Ile Ser Leu Val Ser Lys Asn Gln Val Lys Val
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Phe Leu Asp Asn Ile Ser Phe Trp Lys Leu Phe Gly Phe Glu Asn Ile
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Gln Lys Ile Arg Ile Lys Gly Ile Leu Ser Asn Thr Gln Ser Phe Asn
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1825 1830 1835 1840
Phe Tyr Phe Asp Pro Ile Glu Phe Asn Leu Val Thr Gly Trp Gln Thr
1845 1850 1855
Ile Asn Gly Lys Lys Tyr Tyr Phe Asp Ile Asn Thr Gly Ala Ala Leu
1860 1865 1870
Thr Ser Tyr Lys Ile Ile Asn Gly Lys His Phe Tyr Phe Asn Asn Asp
1875 1880 1885
Gly Val Met Gln Leu Gly Val Phe Lys Gly Pro Asp Gly Phe Glu Tyr
1890 1895 1900

Phe Ala Pro Ala Asn Thr Gln Asn Asn Asn Ile Glu Gly Gln Ala Ile
1905 1910 1915 1920
Val Tyr Gln Ser Lys Phe Leu Thr Leu Asn Gly Lys Lys Tyr Tyr Phe
1925 1930 1935
Asp Asn Asn Ser Lys Ala Val Thr Gly Trp Arg Ile Ile Asn Asn Glu
1940 1945 1950
Lys Tyr Tyr Phe Asn Pro Asn Asn Ala Ile Ala Ala Val Gly Leu Gln
1955 1960 1965
Val Ile Asp Asn Asn Lys Tyr Tyr Phe Asn Pro Asp Thr Ala Ile Ile
1970 1975 1980
Ser Lys Gly Trp Gln Thr Val Asn Gly Ser Arg Tyr Tyr Phe Asp Thr
1985 1990 1995 2000
Asp Thr Ala Ile Ala Phe Asn Gly Tyr Lys Thr Ile Asp Gly Lys His
2005 2010 2015
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2020 2025 2030
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2180 2185 2190
Glu Phe Leu Thr Leu Asn Gly Lys Lys Tyr Tyr Phe Gly Ser Asp Ser
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2245 2250 2255
Thr Ile Glu Arg Asn Asn Phe Tyr Phe Asp Ala Asn Asn Glu Ser Lys
2260 2265 2270
Met Val Thr Gly Val Phe Lys Gly Pro Asn Gly Phe Glu Tyr Phe Ala
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Pro Ala Asn Thr His Asn Asn Asn Ile Glu Gly Gln Ala Ile Val Tyr
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2340 2345 2350
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2370 2375 2380
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2385 2390 2395 2400
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2405 2410 2415
Gly Phe Glu Tyr Phe Ala Pro Ala Asn Thr Asp Ala Asn Asn Ile Glu
2420 2425 2430
Gly Gln Ala Ile Leu Tyr Gln Asn Lys Phe Leu Thr Leu Asn Gly Lys
2435 2440 2445
Lys Tyr Tyr Phe Gly Ser Asp Ser Lys Ala Val Thr Gly Leu Arg Thr

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Thr Ser Ile Ala Ser Thr Gly Tyr Thr Ile Ile Ser Gly Lys His Phe
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Asp Gly Phe Glu Tyr Phe Ala Pro Ala Asn Thr Asp Ala Asn Asn Ile
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Glu Gly Gln Ala Ile Arg Tyr Gln Asn Arg Phe Leu Tyr Leu His Asp
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Ala Asn Gly Tyr Lys Thr Ile Asp Asn Lys Asn Phe Tyr Phe Arg Asn
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Gly Leu Pro Gln Ile Gly Val Phe Lys Gly Ser Asn Gly Phe Glu Tyr
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Val Tyr Tyr Phe Met Pro Asp Thr Ala Met Ala Ala Ala Gly Gly Leu
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<400> 380

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Glu Tyr His Asn Met Ser Glu Asn Thr Val Val Glu Lys Tyr Leu Lys
        35                  40                  45
Leu Lys Asp Ile Asn Ser Leu Thr Asp Ile Tyr Ile Asp Thr Tyr Lys
    50                  55                  60
Lys Ser Gly Arg Asn Lys Ala Leu Lys Lys Phe Lys Glu Tyr Leu Val
65                  70                  75                  80
Thr Glu Val Leu Glu Leu Lys Asn Asn Asn Leu Thr Pro Val Glu Lys
                85                  90                  95
Asn Leu His Phe Val Trp Ile Gly Gly Gln Ile Asn Asp Thr Ala Ile
            100                 105                 110
Asn Tyr Ile Asn Gln Trp Lys Asp Val Asn Ser Asp Tyr Asn Val Asn
        115                 120                 125
Val Phe Tyr Asp Ser Asn Ala Phe Leu Ile Asn Thr Leu Lys Lys Thr
    130                 135                 140
Val Val Glu Ser Ala Ile Asn Asp Thr Leu Glu Ser Phe Arg Glu Asn
145                 150                 155                 160
Leu Asn Asp Pro Arg Phe Asp Tyr Asn Lys Phe Phe Arg Lys Arg Met
                165                 170                 175
Glu Ile Ile Tyr Asp Lys Gln Lys Asn Phe Ile Asn Tyr Tyr Lys Ala
            180                 185                 190
Gln Arg Glu Glu Asn Pro Glu Leu Ile Ile Asp Asp Ile Val Lys Thr
        195                 200                 205
Tyr Leu Ser Asn Glu Tyr Ser Lys Glu Ile Asp Glu Leu Asn Thr Tyr
    210                 215                 220
Ile Glu Glu Ser Leu Asn Lys Ile Thr Gln Asn Ser Gly Asn Asp Val
225                 230                 235                 240
Arg Asn Phe Glu Glu Phe Lys Asn Gly Glu Ser Phe Asn Leu Tyr Glu
                245                 250                 255
Gln Glu Leu Val Glu Arg Trp Asn Leu Ala Ala Ala Ser Asp Ile Leu
            260                 265                 270
Arg Ile Ser Ala Leu Lys Glu Ile Gly Gly Met Tyr Leu Asp Val Asp
        275                 280                 285
Met Leu Pro Gly Ile Gln Pro Asp Leu Phe Glu Ser Ile Glu Lys Pro
    290                 295                 300
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Ser Ser Val Thr Val Asp Phe Trp Glu Met Thr Lys Leu Glu Ala Ile
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Met Lys Tyr Lys Glu Tyr Ile Pro Glu Tyr Thr Ser Glu His Phe Asp
                325                 330                 335
Met Leu Asp Glu Glu Val Gln Ser Ser Phe Glu Ser Val Leu Ala Ser
            340                 345                 350
Lys Ser Asp Lys Ser Glu Ile Phe Ser Ser Leu Gly Asp Met Glu Ala
        355                 360                 365
Ser Pro Leu Glu Val Lys Ile Ala Phe Asn Ser Lys Gly Ile Ile Asn
    370                 375                 380
Gln Gly Leu Ile Ser Val Lys Asp Ser Tyr Cys Ser Asn Leu Ile Val
385                 390                 395                 400
Lys Gln Ile Glu Asn Arg Tyr Lys Ile Leu Asn Asn Ser Leu Asn Pro
                405                 410                 415
Ala Ile Ser Glu Asp Asn Asp Phe Asn Thr Thr Thr Asn Thr Phe Ile
            420                 425                 430
Asp Ser Ile Met Ala Glu Ala Asn Ala Asp Asn Gly Arg Phe Met Met
        435                 440                 445
Glu Leu Gly Lys Tyr Leu Arg Val Gly Phe Phe Pro Asp Val Lys Thr
    450                 455                 460
Thr Ile Asn Leu Ser Gly Pro Glu Ala Tyr Ala Ala Ala Tyr Gln Asp
465                 470                 475                 480
Leu Leu Met Phe Lys Glu Gly Ser Met Asn Ile His Leu Ile Glu Ala
                485                 490                 495
Asp Leu Arg Asn Phe Glu Ile Ser Lys Thr Asn Ile Ser Gln Ser Thr
            500                 505                 510
Glu Gln Glu Met Ala Ser Leu Trp Ser Phe Asp Asp Ala Arg Ala Lys
        515                 520                 525
Ala Gln Phe Glu Glu Tyr Lys Arg Asn Tyr Phe Glu Gly Ser Leu Gly
    530                 535                 540
Glu Asp Asp Asn Leu Asp Phe Ser Gln Asn Ile Val Val Asp Lys Glu
545                 550                 555                 560
Tyr Leu Leu Glu Lys Ile Ser Ser Leu Ala Arg Ser Ser Glu Arg Gly
                565                 570                 575
Tyr Ile His Tyr Ile Val Gln Leu Gln Gly Asp Lys Ile Ser Tyr Glu
            580                 585                 590
Ala Ala Cys Asn Leu Phe Ala Lys Thr Pro Tyr Asp Ser Val Leu Phe
        595                 600                 605
Gln Lys Asn Ile Glu Asp Ser Glu Ile Ala Tyr Tyr Tyr Asn Pro Gly
    610                 615                 620
Asp Gly Glu Ile Gln Glu Ile Asp Lys Tyr Lys Ile Pro Ser Ile Ile
625                 630                 635                 640
Ser Asp Arg Pro Lys Ile Lys Leu Thr Phe Ile Gly His Gly Lys Asp
                645                 650                 655
Glu Phe Asn Thr Asp Ile Phe Ala Gly Phe Asp Val Asp Ser Leu Ser
            660                 665                 670
Thr Glu Ile Glu Ala Ala Ile Asp Leu Ala Lys Glu Asp Ile Ser Pro
        675                 680                 685
Lys Ser Ile Glu Ile Asn Leu Leu Gly Cys Asn Met Phe Ser Tyr Ser
    690                 695                 700
Ile Asn Val Glu Glu Thr Tyr Pro Gly Lys Leu Leu Leu Lys Val Lys
705                 710                 715                 720
Asp Lys Ile Ser Glu Leu Met Pro Ser Ile Ser Gln Asp Ser Ile Ile
                725                 730                 735
Val Ser Ala Asn Gln Tyr Glu Val Arg Ile Asn Ser Glu Gly Arg Arg
            740                 745                 750
Glu Leu Leu Asp His Ser Gly Glu Trp Ile Asn Lys Glu Glu Ser Ile
        755                 760                 765
Ile Lys Asp Ile Ser Ser Lys Glu Tyr Ile Ser Phe Asn Pro Lys Glu
    770                 775                 780
Asn Lys Ile Thr Val Lys Ser Lys Asn Leu Pro Glu Leu Ser Thr Leu
785                 790                 795                 800
Leu Gln Glu Ile Arg Asn Asn Ser Asn Ser Ser Asp Ile Glu Leu Glu
                805                 810                 815
Glu Lys Val Met Leu Thr Glu Cys Glu Ile Asn Val Ile Ser Asn Ile
            820                 825                 830
Asp Thr Gln Ile Val Glu Glu Arg Ile Glu Glu Ala Lys Asn Leu Thr
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Ser Asp Ser Ile Asn Tyr Ile Lys Asp Glu Phe Lys Leu Ile Glu Ser
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Ile Ser Asp Ala Leu Cys Asp Leu Lys Gln Gln Asn Glu Leu Glu Asp
865                 870                 875                 880
Ser His Phe Ile Ser Phe Glu Asp Ile Ser Glu Thr Asp Glu Gly Phe
                885                 890                 895
Ser Ile Arg Phe Ile Asn Lys Glu Thr Gly Glu Ser Ile Phe Val Glu
            900                 905                 910
Thr Glu Lys Thr Ile Phe Ser Glu Tyr Ala Asn His Ile Thr Glu Glu
        915                 920                 925
Ile Ser Lys Ile Lys Gly Thr Ile Phe Asp Thr Val Asn Gly Lys Leu
    930                 935                 940
Val Lys Lys Val Asn Leu Asp Thr Thr His Glu Val Asn Thr Leu Asn
945                 950                 955                 960
Ala Ala Phe Phe Ile Gln Ser Leu Ile Glu Tyr Asn Ser Ser Lys Glu
                965                 970                 975
Ser Leu Ser Asn Leu Ser Val Ala Met Lys Val Gln Val Tyr Ala Gln
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Leu Phe Ser Thr Gly Leu Asn Thr Ile Thr Asp Ala Ala Lys Val Val
        995                 1000                1005
Glu Leu Val Ser Thr Ala Leu Asp Glu Thr Ile Asp Leu Leu Pro Thr
    1010                1015                1020
Leu Ser Glu Gly Leu Pro Ile Ile Ala Thr Ile Ile Asp Gly Val Ser
1025                1030                1035                1040
Leu Gly Ala Ala Ile Lys Glu Leu Ser Glu Thr Ser Asp Pro Leu Leu
                1045                1050                1055
Arg Gln Glu Ile Glu Ala Lys Ile Gly Ile Met Ala Val Asn Leu Thr
            1060                1065                1070
Thr Ala Thr Thr Ala Ile Ile Thr Ser Ser Leu Gly Ile Ala Ser Gly
        1075                1080                1085
Phe Ser Ile Leu Leu Val Pro Leu Ala Gly Ile Ser Ala Gly Ile Pro
    1090                1095                1100
Ser Leu Val Asn Asn Glu Leu Val Leu Arg Asp Lys Ala Thr Lys Val
1105                1110                1115                1120
Val Asp Tyr Phe Lys His Val Ser Leu Val Glu Thr Glu Gly Val Phe
                1125                1130                1135
Thr Leu Leu Asp Asp Lys Ile Met Met Pro Gln Asp Asp Leu Val Ile
            1140                1145                1150
Ser Glu Ile Asp Phe Asn Asn Asn Ser Ile Val Leu Gly Lys Cys Glu
        1155                1160                1165
Ile Trp Arg Met Glu Gly Gly Ser Gly His Thr Val Thr Asp Asp Ile
    1170                1175                1180
Asp His Phe Phe Ser Ala Pro Ser Ile Thr Tyr Arg Glu Pro His Leu
1185                1190                1195                1200
Ser Ile Tyr Asp Val Leu Glu Val Gln Lys Glu Glu Leu Asp Leu Ser
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Lys Asp Leu Met Val Leu Pro Asn Ala Pro Asn Arg Val Phe Ala Trp
            1220                1225                1230
Glu Thr Gly Trp Thr Pro Gly Leu Arg Ser Leu Glu Asn Asp Gly Thr
        1235                1240                1245
Lys Leu Leu Asp Arg Ile Arg Asp Asn Tyr Glu Gly Glu Phe Tyr Trp
    1250                1255                1260
Arg Tyr Phe Ala Phe Ile Ala Asp Ala Leu Ile Thr Thr Leu Lys Pro
1265                1270                1275                1280
Arg Tyr Glu Asp Thr Asn Ile Arg Ile Asn Leu Asp Ser Asn Thr Arg
                1285                1290                1295
Ser Phe Ile Val Pro Ile Ile Thr Thr Glu Tyr Ile Arg Glu Lys Leu
            1300                1305                1310
Ser Tyr Ser Phe Tyr Gly Ser Gly Gly Thr Tyr Ala Leu Ser Leu Ser
        1315                1320                1325
Gln Tyr Asn Met Gly Ile Asn Ile Glu Leu Ser Glu Ser Asp Val Trp
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Ile Ile Asp Val Asp Asn Val Val Arg Asp Val Thr Ile Glu Ser Asp
1345                1350                1355                1360
Lys Ile Lys Lys Gly Asp Leu Ile Glu Gly Ile Leu Ser Thr Leu Ser
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Ile Glu Glu Asn Lys Ile Ile Leu Asn Ser His Glu Ile Asn Phe Ser
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Gly Glu Val Asn Gly Ser Asn Gly Phe Val Ser Leu Thr Phe Ser Ile
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Asn His Ile Gln Gln Lys Ile Asp Tyr Ile Gly Phe Asn Ser Glu Leu
                1445                1450                1455
Gln Lys Asn Ile Pro Tyr Ser Phe Val Asp Ser Glu Gly Lys Glu Asn
            1460                1465                1470
Gly Phe Ile Asn Gly Ser Thr Lys Glu Gly Leu Phe Val Ser Glu Leu
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Pro Asp Val Val Leu Ile Ser Lys Val Tyr Met Asp Asp Ser Lys Pro
    1490                1495                1500
Ser Phe Gly Tyr Tyr Ser Asn Asn Leu Lys Asp Val Lys Val Ile Thr
1505                1510                1515                1520
Lys Asp Asn Val Asn Ile Leu Thr Gly Tyr Tyr Leu Lys Asp Asp Ile
                1525                1530                1535
Lys Ile Ser Leu Ser Leu Thr Leu Gln Asp Glu Lys Thr Ile Lys Leu
            1540                1545                1550
Asn Ser Val His Leu Asp Glu Ser Gly Val Ala Glu Ile Leu Lys Phe
        1555                1560                1565
Met Asn Arg Lys Gly Asn Thr Asn Thr Ser Asp Ser Leu Met Ser Phe
    1570                1575                1580
Leu Glu Ser Met Asn Ile Lys Ser Ile Phe Val Asn Phe Leu Gln Ser
1585                1590                1595                1600
Asn Ile Lys Phe Ile Leu Asp Ala Asn Phe Ile Ile Ser Gly Thr Thr
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Ser Ile Gly Gln Phe Glu Phe Ile Cys Asp Glu Asn Asp Asn Ile Gln
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Pro Tyr Phe Ile Lys Phe Asn Thr Leu Glu Thr Asn Tyr Thr Leu Tyr
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Val Gly Asn Arg Gln Asn Met Ile Val Glu Pro Asn Tyr Asp Leu Asp
    1650                1655                1660
Asp Ser Gly Asp Ile Ser Ser Thr Val Ile Asn Phe Ser Gln Lys Tyr
1665                1670                1675                1680
Leu Tyr Gly Ile Asp Ser Cys Val Asn Lys Val Val Ile Ser Pro Asn
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Ile Tyr Thr Asp Glu Ile Asn Ile Thr Pro Val Tyr Glu Thr Asn Asn
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Thr Tyr Pro Glu Val Ile Val Leu Asp Ala Asn Tyr Ile Asn Glu Lys
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Asp Gly Asn Asp Phe Ile Leu Met Ser Thr Ser Glu Glu Asn Lys Val
1745                1750                1755                1760
Ser Gln Val Lys Ile Arg Phe Val Asn Val Phe Lys Asp Lys Thr Leu
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Ala Asn Lys Leu Ser Phe Asn Phe Ser Asp Lys Gln Asp Val Pro Val
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Ser Glu Ile Ile Leu Ser Phe Thr Pro Ser Tyr Tyr Glu Asp Gly Leu
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Ile Gly Tyr Asp Leu Gly Leu Val Ser Leu Tyr Asn Glu Lys Phe Tyr
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Ile Asn Asn Phe Gly Met Met Val Ser Gly Leu Ile Tyr Ile Asn Asp
1825                1830                1835                1840
Ser Leu Tyr Tyr Phe Lys Pro Pro Val Asn Asn Leu Ile Thr Gly Phe
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Val Thr Val Gly Asp Asp Lys Tyr Tyr Phe Asn Pro Ile Asn Gly Gly
            1860                1865                1870
Ala Ala Ser Ile Gly Glu Thr Ile Ile Asp Asp Lys Asn Tyr Tyr Phe
        1875                1880                1885
Asn Gln Ser Gly Val Leu Gln Thr Gly Val Phe Ser Thr Glu Asp Gly
    1890                1895                1900
Phe Lys Tyr Phe Ala Pro Ala Asn Thr Leu Asp Glu Asn Leu Glu Gly
1905                1910                1915                1920
Glu Ala Ile Asp Phe Thr Gly Lys Leu Ile Ile Asp Glu Asn Ile Tyr
                1925                1930                1935
Tyr Phe Asp Asp Asn Tyr Arg Gly Ala Val Glu Trp Lys Glu Leu Asp
            1940                1945                1950
Gly Glu Met His Tyr Phe Ser Pro Glu Thr Gly Lys Ala Phe Lys Gly
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    1970                1975                1980
Met Gln Lys Gly Phe Val Ser Ile Asn Asp Asn Lys His Tyr Phe Asp
1985                1990                1995                2000
Asp Ser Gly Val Met Lys Val Gly Tyr Thr Glu Ile Asp Gly Lys His
                2005                2010                2015
Phe Tyr Phe Ala Glu Asn Gly Glu Met Gln Ile Gly Val Phe Asn Thr
            2020                2025                2030
Glu Asp Gly Phe Lys Tyr Phe Ala His His Asn Glu Asp Leu Gly Asn
        2035                2040                2045
Glu Glu Gly Glu Glu Ile Ser Tyr Ser Gly Ile Leu Asn Phe Asn Asn
    2050                2055                2060
Lys Ile Tyr Tyr Phe Asp Asp Ser Phe Thr Ala Val Val Gly Trp Lys
2065                2070                2075                2080
Asp Leu Glu Asp Gly Ser Lys Tyr Tyr Phe Asp Glu Asp Thr Ala Glu
                2085                2090                2095
Ala Tyr Ile Gly Leu Ser Leu Ile Asn Asp Gly Gln Tyr Tyr Phe Asn
            2100                2105                2110
Asp Asp Gly Ile Met Gln Val Gly Phe Val Thr Ile Asn Asp Lys Val
        2115                2120                2125
Phe Tyr Phe Ser Asp Ser Gly Ile Ile Glu Ser Gly Val Gln Asn Ile
    2130                2135                2140
Asp Asp Asn Tyr Phe Tyr Ile Asp Asp Asn Gly Ile Val Gln Ile Gly
2145                2150                2155                2160
Val Phe Asp Thr Ser Asp Gly Tyr Lys Tyr Phe Ala Pro Ala Asn Thr
                2165                2170                2175
Val Asn Asp Asn Ile Tyr Gly Gln Ala Val Glu Tyr Ser Gly Leu Val
            2180                2185                2190
Arg Val Gly Glu Asp Val Tyr Tyr Phe Gly Glu Thr Tyr Thr Ile Glu
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Thr Gly Trp Ile Tyr Asp Met Glu Asn Glu Ser Asp Lys Tyr Tyr Phe
    2210                2215                2220
Asn Pro Glu Thr Lys Lys Ala Cys Lys Gly Ile Asn Leu Ile Asp Asp
2225                2230                2235                2240
Ile Lys Tyr Tyr Phe Asp Glu Lys Gly Ile Met Arg Thr Gly Leu Ile
                2245                2250                2255
Ser Phe Glu Asn Asn Asn Tyr Tyr Phe Asn Glu Asn Gly Glu Met Gln
            2260                2265                2270
Phe Gly Tyr Ile Asn Ile Glu Asp Lys Met Phe Tyr Phe Gly Glu Asp
        2275                2280                2285
Gly Val Met Gln Ile Gly Val Phe Asn Thr Pro Asp Gly Phe Lys Tyr
    2290                2295                2300
Phe Ala His Gln Asn Thr Leu Asp Glu Asn Phe Glu Gly Glu Ser Ile
2305                2310                2315                2320
Asn Tyr Thr Gly Trp Leu Asp Leu Asp Glu Lys Arg Tyr Tyr Phe Thr
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Asp Glu Tyr Ile Ala Ala Thr Gly Ser Val Ile Ile Asp Gly Glu Glu
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<223> Xaa = Gly

<220>
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<223> Xaa = Ser, Gly, Asp, or Thr

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<223> Xaa = Ser, His, or Ile

<220>
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<223> Xaa = Glu, Gln, or Ile

<400> 382
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<210> 383
<211> 17
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<220>
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<223> Xaa = Lys, or Arg

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<223> Xaa = Gly, or Glu

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<223> Xaa = Ser, or Arg

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<223> Xaa = Ile, Asp, or Tyr

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<223> Xaa = Tyr

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<223> Xaa = Phe, Leu, or absent

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<223> Xaa = Gly, or absent

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<223> Xaa = Met, or absent

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<223> Xaa = Asp, or absent

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<223> Xaa = Val, or absent

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Xaa

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<223> Xaa = Ser, or Glu

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<223> Xaa = Ile, Val, or Thr

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<223> Xaa = Phe, Lys, or Asn

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<223> Xaa = Lys, or absent

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<223> Xaa = Ile, Asn, or absent

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<223> Xaa = Tyr, or absent

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<223> Xaa = Ala or Thr

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<400> 385
Xaa Xaa Xaa
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<211> 9
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<223> Xaa = Thr, or Ser

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<223> Xaa = Leu, Ala, or Tyr

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<223> Xaa = Pro, Phe, or Ser

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<222> (8)...(8)
<223> Xaa = Leu, Phe, or Arg

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<222> (9)...(9)
<223> Xaa = Thr, or Ala

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1   5

<210> 387
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<213> Artificial Sequence

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<223> Xaa = Phe

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<223> Xaa = Asn, or Thr

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<223> Xaa = Phe

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<223> Xaa = Thr, Ser, Asn, or Asp

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<223> Xaa = His, Tyr, or Phe

<220>
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<223> Xaa = Asp, Val, Ala, or Tyr

<400> 387
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1   5

<210> 388
<211> 8
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<400> 388
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1   5

<210> 389
<211> 24
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<220>
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<223> Xaa = Lys, or Arg

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<223> Xaa = Tyr, Leu, or absent

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<223> Xaa = Val, or absent

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

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<223> Xaa = Ser, Asp, or Thr

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<223> Xaa = Ile, or Val

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<400> 390
Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1   5

<210> 391
<211> 3
<212> PRT
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<223> Xaa = Ala, Thr, or Val

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<223> Xaa = Ser

<400> 391
Xaa Xaa Xaa
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<210> 392
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<213> Artificial Sequence

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<223> Xaa = Gln, Lys, or absent

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<223> Xaa = Leu, Pro, Ser, or absent

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

<210> 393
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 1   5   10

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<211> 9
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 1   5

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<223> Xaa = Arg, Lys, Thr, or Ser

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 1   5   10   15

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<212> PRT
<213> Artificial Sequence

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<223> Xaa = Trp, His, Asn, Phe, Ser, or Asp

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<223> Xaa = Tyr, or absent

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1   5

<210> 397
<211> 3
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