(12) STANDARD PATENT (11) Application No. **AU 2016211783 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Human antibodies to Ebola virus glycoprotein

(51) International Patent Classification(s)
C07K 16/10 (2006.01)

(21) Application No: **2016211783** (22) Date of Filing: **2016.01.25**

(87) WIPO No: **WO16/123019**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/161,356	**2015.05.14**	**US**
62/107,581	**2015.01.26**	**US**
62/245,703	**2015.10.23**	**US**

(43) Publication Date: **2016.08.04**
(44) Accepted Journal Date: **2021.07.22**

(71) Applicant(s)
Regeneron Pharmaceuticals, Inc.

(72) Inventor(s)
Kyratsous, Christos;Olson, William;Mason, Peter;Stahl, Neil

(74) Agent / Attorney
AJ PARK, Level 24, Tower 2, Darling Park 201 Sussex St, Sydney, NSW, 2000, AU

(56) Related Art
WO 2009094755 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 August 2016 (04.08.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/123019 A1

(51) International Patent Classification:
C07K 16/10 (2006.01)

(21) International Application Number:
PCT/US2016/014720

(22) International Filing Date:
25 January 2016 (25.01.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/107,581	26 January 2015 (26.01.2015)	US
62/161,356	14 May 2015 (14.05.2015)	US
62/245,703	23 October 2015 (23.10.2015)	US

(71) Applicant: **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, New York 10591-6707 (US).

(72) Inventors: **KYRATSOUS, Christos**; c/o Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, New York 10591 (US). **OLSON, William**; c/o Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, New York 10591 (US). **MASON, Peter**; c/o Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, New York 10591 (US). **STAHL, Neil**; c/o Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, New York 10591 (US).

(74) Agents: **CROWLEY-WEBER, Cara L.** et al.; Brownstein Hyatt Farber Schreck, LLP, 410 Seventeenth Street, Suite 2200, Denver, Colorado 80202 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

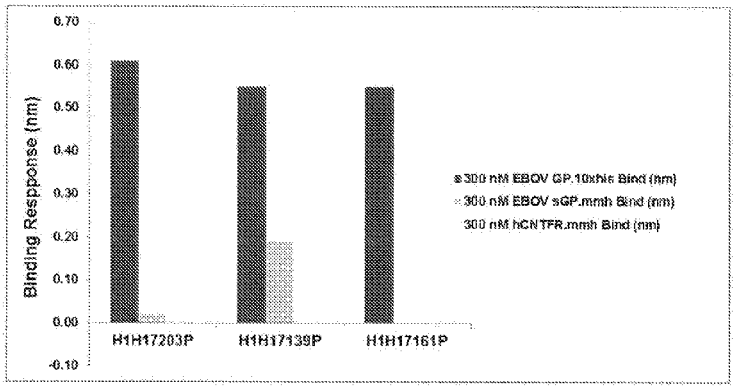
Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) Title: HUMAN ANTIBODIES TO EBOLA VIRUS GLYCOPROTEIN

Figure 2: Interaction of H1H17203, H1H17139P and H1H17161P with Ebola GP.10xhis and Ebola soluble GP (sGP.mmh) at 25 °C



Octet HTX binding signals for each of the Ebola GP antibodies to 300nM Ebola GP.10xhis (black), Ebola soluble sGP.mmh (dark grey), and the irrelevant, negative control protein hCNTFR.mmh (light gray).

(57) Abstract: The present invention provides monoclonal antibodies, or antigen-binding fragments thereof, that bind to Ebola virus glycoproteins, pharmaceutical compositions comprising the antibodies and methods of use. The antibodies of the invention are useful for inhibiting or neutralizing Ebola virus activity, thus providing a means of treating or preventing Ebola virus infection in humans. In some embodiments, the invention provides for use of one or more antibodies that bind to the Ebola virus for preventing viral attachment and/or entry into host cells. The antibodies of the invention may be used prophylactically or therapeutically and may be used alone or in combination with one or more other anti-viral agents or vaccines.

WO 2016/123019 A1

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

HUMAN ANTIBODIES TO EBOLA VIRUS GLYCOPROTEIN

FIELD OF THE INVENTION

[0001] The present invention generally relates to antibodies that bind to Ebola virus glycoprotein, pharmaceutical compositions comprising these antibodies and methods of use thereof.

BACKGROUND

[0002] Ebola virus (EBOV) and related filoviruses cause severe viral hemorrhagic fever in humans and non-human primates, with a fatality rate of up to about 90% in human outbreaks. (Murin, C.D. *et al.*, (2014), Proc Natl Acad Sci USA, 111(48):17182-17187). The immune mechanisms that mediate protection are under investigation, but to date, no treatments have been approved for human use.

[0003] The Ebola virus glycoprotein (GP) is the only protein present on the surface of the virus and on infected cells. It is presumed to be responsible for binding and fusion of the virus with host cells. The GP exists in several forms. These GPs are encoded in two open reading frames. The unedited GP mRNA produces a non-structural secreted, soluble GP (sGP) that is synthesized early in the course of infection (Volchkova, *et al.* (1995), Virology 214:421-430; Volchkova, VA *et al.*, (1998), Virology 250:408-414; Sanchez, *et al.* (1996), Proc Natl Acad Sci USA, 93:3602-3607; Sanchez, *et al.* (1999) J. Infect. Dis. 179 (suppl. 1, S164)). The sGP forms dimers (Volchkova, *et al.* (1995), Virology 214:421-430; Falzarano, D. *et al.*, Chembiochem (2006), 7:1605-1611) and high amounts are detected in the blood of patients and experimentally infected animals (Sanchez, *et al.* (1996), Proc Natl Acad Sci USA, 93:3602-3607; Dolnik, O. *et al.*, (2004), EMBO J 23:2175-2184).

[0004] Later in infection, an edited mRNA is generated, acquiring coding capacity from a second open reading frame. This edited mRNA encodes a form of GP that contains a transmembrane (TM) domain that permits this form of GP to be tethered to the plasma membrane of the cell, and incorporated into virions where it serves as the functional host cell receptor-binding protein/fusion protein. During biosynthesis of this form of GP, the protein is proteolytically processed into two products that are held together by disulfide bonds. The amino terminal product is referred to as GP1 (140 kDa) and the carboxy-terminal cleavage product is referred to as GP2 (26 kDa) (Sanchez, *et al.* (1998), J. Virol. 72:6442-6447).

[0005] The Ebola virus GP (EBOV GP) may be a target for protective antibodies, but the role of antibodies in disease resistance has been controversial. Negligible serum titers of neutralizing antibodies in convalescent patients together with inconsistent results in achieving protection with experimental transfer of immune sera to animals has resulted in speculation as to the role of neutralizing antibodies in recovery from infection (Peters, CJ and LeDuc, JW, (1999), J. Infect. Dis. 179 Suppl 1; Mikhailov, VV, (1994), Vopr. Virusol. 39:82; Xu, L. *et al.,* (1998), Nature

Med. 4: 37). However, in the more recent outbreak of Ebola virus, a few patients who contracted the disease and who were treated with a cocktail of monoclonal antibodies (ZMapp) specific for the viral GP recovered from the disease. Moreover, other patients that were treated with the serum from these patients and from other patients who survived after acquiring the infection, also had positive outcomes.

[0006] Several antibodies that bind Ebola virus GP have been described (See for example, US Patent Nos. 6630144, 6875433, 7335356 and 8513391. See also EP1539238, EP2350270 and EP8513391).

[0007] While technological advances have improved the ability to produce improved Ebola virus antigen(s) vaccine compositions, there remains a need to provide additional sources of protection to address emerging strains of Ebola virus. Several candidate therapeutics against Ebola virus are currently under evaluation, including post exposure vaccines (Feldman, H, *et al.* (2007), PLos Pathog 3(1):e2), small molecule inhibitors (Cote, M. *et al*. (2011), Nature, 477(7364):344-348; Johansen, LM, *et al*. (2013), Sci Transl Med 5(190):190ra179; Warren, TK, *et al.,* (2014), Nature, 508(7496):402-405), siRNA-based therapeutics (Geisbert, TW, *et al*., (2006), J. Infect Dis. 193(12):1650-1657; Geisbert, TW *et al.,* (2010), Lancet 375(9729):1896-1905), and monoclonal antibodies (Saphire, EO, (2013), Immunotherapy 5(11):1221-1233; Wong, G. et al. (2014), Trends Microbiol. 22(8):456-463; Qiu, X *et al.,* (2014), Hum. Vaccin. Immunother. 10(4):964-967). Passive administration of antibodies to non-human primates has proven to be efficacious (Dye, JM., *et al.,* (2012), Proc Natl Acad Sci USA 109(13):5034-5039). More recently, a cocktail of three antibodies (ZMapp) is currently being produced in tobacco plants and is in development for human use (Qiu, X. *et al.,* (2014), Nature 514(7520):47-53).

[0008] While the idea of a vaccine composition comprising the antigen of interest (*e.g.* the GP) to generate neutralizing antibodies in a patient is generally thought to be a good approach, it may not be advantageous to use in patients who have already been exposed to the virus, since it would take several weeks for the body to respond to the vaccine composition. By that point in time, the patient may have already succumbed to the viral infection, depending on the level of care and palliative therapy available. In these patients, or in any patient who is not able to mount an effective antibody response, it may be more beneficial to provide a composition already containing protective antibodies that may target epitopes common to a particular strain of EBOV, or to a variety of strains.

[0009] Accordingly, there is still a need in the art to identify new antibodies, which can be used to prevent or treat an Ebola virus infection. It is an object of the invention to go at least some way towards meeting this need; and/or to at least provide the public with a useful choice.

BRIEF SUMMARY OF THE INVENTION

[0009A] In a first aspect, the invention relates to an isolated recombinant antibody or antigen-binding fragment thereof that specifically binds to Ebola virus (EBOV) and/or an Ebola virus glycoprotein (EBOV-GP), wherein the antibody or antigen-binding fragment thereof comprises:

(i) an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30; and an LCDR3 amino acid sequence of SEQ ID NO: 32;

(ii) an HCDR1 amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 70; an HCDR3 amino acid sequence of SEQ ID NO: 72; an LCDR1 amino acid sequence of SEQ ID NO: 76; an LCDR2 amino acid sequence of SEQ ID NO: 78; and an LCDR3 amino acid sequence of SEQ ID NO: 80; or

(iii) an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158; and an LCDR3 amino acid sequence of SEQ ID NO: 160.

[0009B] In a second aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof that binds to the same epitope on EBOV and/or EBOV GP as a reference antibody or antigen-binding fragment comprising:

(i) an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30; and an LCDR3 amino acid sequence of SEQ ID NO: 32;

(ii) an HCDR1 amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 70; an HCDR3 amino acid sequence of SEQ ID NO: 72; an LCDR1 amino acid sequence of SEQ ID NO: 76; an LCDR2 amino acid sequence of SEQ ID NO: 78; and an LCDR3 amino acid sequence of SEQ ID NO: 80; or

(iii) an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158; and an LCDR3 amino acid sequence of SEQ ID NO: 160.

[0009C] In a third aspect, the invention relates to a method of neutralizing infectious EBOV, the method comprising exposing a cell infected with EBOV to a composition comprising one or more anti-EBOV antibodies or antigen-binding fragments thereof according to the first or second aspect, wherein the exposing results in enhanced protection of the cell from virus infection, or from cell death.

[0009D] In a fourth aspect, the invention relates to use of a composition comprising one or more anti-EBOV antibodies or antigen-binding fragments thereof according to the first or second

aspect in the manufacture of a medicament for use in a method of neutralizing infectious EBOV, the method comprising exposing a cell infected with EBOV to the composition, wherein the exposing results in enhanced protection of the cell from virus infection, or from cell death.

[0009E] In a fifth aspect, the invention relates to a pharmaceutical composition comprising one or more isolated monoclonal antibodies or antigen-binding fragments thereof that bind specifically to EBOV according to the first or second aspect and a pharmaceutically acceptable carrier or diluent.

[0009F] In a sixth aspect, the invention relates to a pharmaceutical composition comprising (a) a first anti-EBOV antibody or an antigen-binding fragment thereof according to the first or second aspect; (b) a second anti-EBOV antibody or antigen-binding fragment thereof; and (c) a third anti-EBOV antibody or antigen-binding fragment thereof, wherein the first antibody binds to, or interacts with, a first epitope on EBOV and the second and/or third antibody binds to, or interact(s) with a different epitope on EBOV, and (d) a pharmaceutically acceptable carrier or diluent.

[0009G] In a seventh aspect, the invention relates to a pharmaceutical composition comprising a first isolated monoclonal antibody or an antigen-binding fragment thereof that binds specifically to EBOV, wherein the first isolated monoclonal antibody or an antigen-binding fragment thereof comprises an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30 and an LCDR3 amino acid sequence of SEQ ID NO: 32, and a pharmaceutically acceptable carrier or diluent.

[0009H] In an eighth aspect, the invention relates to an isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an HCVR, and an LCVR of an antibody according to the first or second aspect.

[0009I] In a ninth aspect, the invention relates to a vector comprising the polynucleotide according to the eighth aspect.

[0009J] In a tenth aspect, the invention relates to a cell expressing the vector according to the ninth aspect.

[0009K] In an eleventh aspect, the invention relates to a method of preventing, treating or ameliorating at least one symptom of EBOV infection, or of decreasing the frequency or severity of at least one symptom of EBOV infection, the method comprising administering an antibody or antigen-binding fragment thereof according to the first or second aspect or a pharmaceutical composition according to any one of the fifth to seventh aspects to a subject in need thereof

[0009L] In a twelfth aspect, the invention relates to use of an antibody or antigen-binding fragment according the first or second aspect, or a pharmaceutical composition according to any one of the fifth to seventh aspects, in the manufacture of a medicament for use in a method of preventing, treating or ameliorating at least one symptom of EBOV infection, or of decreasing

the frequency or severity of at least one symptom of EBOV infection, the method comprising administering the antibody or antigen-binding fragment thereof or the pharmaceutical composition to a subject in need thereof.

[0009M] In a thirteenth aspect, the invention relates to a method of increasing survival, or the likelihood of survival, of a subject suffering from infection with EBOV, or a subject exposed to EBOV, or at risk for exposure to, or for acquiring EBOV, the method comprising administering at least one antibody or antigen-binding fragment thereof according to the first or second aspect or a pharmaceutical composition according to any one of the fifth to seventh aspects to a subject in need thereof.

[0009N] In a fourteenth aspect, the invention relates to use of an antibody or antigen-binding fragment thereof according to the first or second aspect or a pharmaceutical composition according to any one of the fifth to seventh aspects, in the manufacture of a medicament for use in a method of increasing survival, or the likelihood of survival of a subject suffering from infection with EBOV, or a subject exposed to EBOV, or at risk for exposure to, or for acquiring EBOV, the method comprising administering at least one antibody or antigen-binding fragment, or the pharmaceutical composition to a subject in need thereof.

BRIEF DESCRIPTION

[0010] The present description includes antibodies and antigen-binding fragments thereof that bind Ebola virus (EBOV) glycoprotein (GP). The antibodies of the present description are useful for inhibiting or neutralizing the activity of Ebola virus. In some embodiments, the antibodies are useful for blocking attachment of the Ebola virus to the host cell and/or for preventing the entry of the Ebola virus into host cells. In some embodiments, the antibodies function by inhibiting the cell-to-cell transmission of the virus, or by killing Ebola virus-infected cells, reducing production of pathogenic virus. In certain embodiments, the antibodies are useful in preventing, treating or ameliorating at least one symptom of Ebola virus infection in a subject. In certain embodiments, the antibodies may be administered prophylactically or therapeutically to a subject having, or at risk of acquiring, an Ebola virus infection. In certain embodiments, compositions containing at least one antibody of the description may be administered to a subject for whom a vaccine is contra-indicated, or for whom a vaccine is less efficacious, for example, an elderly patient, a very young patient, a patient who may be allergic to any one or more components of a vaccine, or an immunocompromised patient who may be non-responsive to the immunogens in a vaccine. In certain embodiments, compositions containing at least one antibody of the description may be administered to medical staff, hospitalized patients or nursing home residents or other high-risk patients during an Ebola virus outbreak. In certain embodiments, compositions containing at least one antibody of the description may be administered as a first line treatment to patients who have already been exposed to an Ebola virus.

[0011] The antibodies of the description 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 increase persistence in the host or to eliminate residual effector functions (Reddy *et al.*, 2000, J. Immunol. 164:1925-1933). In certain embodiments, the antibodies may be bispecific.

[0012] Described herein are isolated recombinant monoclonal antibodies or antigen-binding fragments thereof that bind specifically to the EBOV GP.

[0013] In one embodiment, described is an isolated recombinant antibody or antigen-binding fragment thereof that specifically binds to Ebola virus (EBOV) and/or an Ebola virus glycoprotein (EBOV-GP), wherein the antibody has one or more of the following characteristics:

(a) comprises three heavy chain complementarity determining regions (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, 66, 146, 2, 34, 50, 82, 98, 114, 130, 162, 178, 194, 210, 226, 242, 258, 274, 290, and 306; and 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, 74, 154, 10, 42, 58, 90, 106, 122, 138, 170, 186, 202, 218, 234, 250, 266, 282, and 298;

(b) is a fully human monoclonal antibody;

(c) binds to EBOV, or a virus like particle (VLP) expressing an EBOV-GP with a dissociation constant (K_D) of less than 10^{-7}M, as measured in a surface plasmon resonance assay;

(d) demonstrates at least a 3 fold increase in dissociative half-life (t½) at pH 5 or pH 6 relative to pH 7.4;

(e) demonstrates neutralization of Zaire Ebola virus with an IC50 ranging from about 10^{-11} M to about 10^{-9} M;

(f) demonstrates binding to cells expressing the EBOV-GP triggering antibody-dependent cellular cytotoxicity;

(g) cross reacts with one or more strains of EBOV selected from the group consisting of Zaire.2014, Zaire.1995, Sudan, Bundibugyo and Cote d'Ivoire;

(h) binds to soluble GP (sGP);

(i) cross-competes with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

[0014] In one embodiment, described is an isolated recombinant antibody or antigen-binding fragment thereof that specifically binds to EBOV and/or an Ebola virus glycoprotein (EBOV GP), wherein the antibody has two or more of the following characteristics:

(a) is a fully human monoclonal antibody;

(b) binds to EBOV, or a virus like particle (VLP) expressing an EBOV GP with a dissociation constant (K_D) of less than 10^{-7}M, as measured in a surface plasmon resonance assay;

(c) demonstrates at least a 3 fold increase in dissociative half-life (t½) at pH 5 or pH 6 relative to pH 7.4;

(d) demonstrates neutralization of Zaire Ebola virus with an IC_{50} ranging from about 10^{-11} M to about 10^{-9} M;

(e) demonstrates binding to cells expressing the EBOV GP triggering antibody-dependent cellular cytotoxicity;

(f) cross reacts with one or more strains of EBOV selected from the group consisting of Zaire.2014, Zaire.1995, Sudan, Bundibugyo and Cote d'Ivoire;

(g) binds to soluble GP (sGP);

(h) cross-competes with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

[0015] Exemplary anti-Ebola virus GP antibodies of the present description are listed in Tables 1 and 2 herein. Table 1 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of exemplary anti-Ebola virus GP antibodies. Table 2 sets forth the nucleic acid sequence identifiers of the HCVRs, LCVRs, HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 of the exemplary anti-Ebola virus GP antibodies.

[0016] The present description includes antibodies, or antigen-binding fragments thereof, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0017] The present description also includes antibodies, or antigen-binding fragments thereof, comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0018] The present description also includes antibodies, or antigen-binding fragments thereof, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1. According to certain embodiments, the present description includes antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-Ebola virus GP antibodies listed in Table 1.

[0019] In one embodiment, the isolated antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26, 66/74, 146/154, 2/10, 34/42, 50/58, 82/90, 98/106, 114/122, 130/138, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298 and 306/282.

[0020] In one embodiment, the isolated antibody or antigen-binding fragment comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 68, 148, 4, 36, 52, 84, 100, 116, 132, 164, 180, 196, 212, 228, 244, 260, 276, 292 and 308;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 70, 150, 6, 38, 54, 86, 102, 118, 134, 166, 182, 198, 214, 230, 246, 262, 278, 294 and 310;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 72, 152, 8, 40, 56, 88, 104, 120, 136, 168, 184, 200, 216, 232, 248, 264, 280, 296 and 312;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 76, 156, 12, 44, 60, 92, 108, 124, 140, 172, 188, 204, 220, 236, 252, 268, 284 and 300;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 78, 158, 14, 46, 62, 94, 110, 126, 142, 174, 190, 206, 222, 238, 254, 270, 286 and 302;

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 32, 80, 160, 16, 48, 64, 96, 112, 128, 144, 176, 192, 208, 224, 240, 256, 272, 288 and 304.

[0021] In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 18/26 (H1H17139P), 66/74 (H1H17161P) and 146/154 (H1H17203P).

[0022] The present description also includes antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0023] The present description also includes antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0024] The present description also includes antibodies, or antigen-binding fragments thereof, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0025] The present description also includes antibodies, or antigen-binding fragments thereof, comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0026] The present description also includes antibodies, or antigen-binding fragments thereof, comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0027] The present description also includes antibodies, or antigen-binding fragments thereof, comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0028] The present description also includes antibodies, or antigen-binding fragments thereof, comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 1 paired with any of the LCDR3 amino acid sequences listed in Table 1. According to certain embodiments, the present description includes antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-Ebola virus GP antibodies listed in Table 1. In certain embodiments, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 24/32 (*e.g.*, H1H17139P), 72/80 (*e.g.*, H1H17161P), and 152/160 (*e.g.*, H1H17203P).

[0029] The present description also includes antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-Ebola virus GP antibodies listed in Table 1. In certain embodiments, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set is selected from the group consisting of SEQ ID NOs: 20-22-24-28-30-32 (*e.g.*, H1H17139P), 68-70-72-76-78-80 (*e.g.*, H1H17161P); and 148-150-152-156-158-160 (*e.g.*, H1H17203P).

[0030] In a related embodiment, the present description includes antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-Ebola virus GP antibodies listed in Table 1. For example, the present description includes antibodies, or antigen-binding fragments thereof, comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26 (e.g., H1H17139P), 66/74 (*e.g.*, H1H17161P); and 146/154 (*e.g.*, H1H17203P). Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the

boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0031] The present description includes anti-Ebola virus antibodies having a modified glycosylation pattern. In some embodiments, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0032] The present description also includes for antibodies and antigen-binding fragments thereof that compete for specific binding to Ebola virus with an antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

[0033] The present description also includes antibodies and antigen-binding fragments thereof that cross-compete for binding to Ebola virus with a reference antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

[0034] The present description also includes isolated antibodies and antigen-binding fragments thereof that block Ebola virus attachment to, and/or entry into a host cell.

[0035] In certain embodiments, the antibodies or antigen-binding fragments of the present description are bispecific comprising a first binding specificity to a first epitope in the Ebola virus and a second binding specificity to a second epitope in the Ebola virus, wherein the first and second epitopes are distinct and non-overlapping. In certain embodiments the bispecific may comprise a first arm that binds to an epitope in the viral glycoprotein and a second arm that binds to an epitope in a different viral antigen.

[0036] Also described are nucleic acid molecules encoding anti-Ebola virus antibodies or portions thereof. For example, the present description includes nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0037] The present description also includes nucleic acid molecules encoding any of the LCVR amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0038] The present description also includes nucleic acid molecules encoding any of the HCDR1 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0039] The present description also includes nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0040] The present description also includes nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0041] The present description also includes nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0042] The present description also includes nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0043] The present description also includes nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 1; in certain embodiments the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0044] The present description also includes nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-

Ebola virus GP antibodies listed in Table 1.

[0045] The present description also includes nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (*i.e.*, LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary anti-Ebola virus GP antibodies listed in Table 1.

[0046] The present description also includes nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 1, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 1. In certain embodiments, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain embodiments according to this embodiment of the description, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-Ebola virus GP antibody listed in Table 1.

[0047] The present description includes nucleic acid molecules encoding any of the heavy chain amino acid sequences listed in Table 1. The present description also includes nucleic acid molecules encoding any of the light chain amino acid sequences listed in Table 1.

[0048] In a related embodiment, the present description includes recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-Ebola virus GP antibody. For example, the present description includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 1. Also described are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced.

[0049] Also described is a pharmaceutical composition comprising one or more isolated monoclonal antibodies or antigen-binding fragments thereof which specifically bind to Ebola virus GP and a pharmaceutically acceptable carrier or diluent. The one or more isolated antibodies comprise an HCVR/LCVR amino acid sequence pair selected from the group consisting of the HCVR and LCVR sequences listed in Table 1. In one embodiment, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 18/26, 66/74, 146/154, 2/10, 34/42, 50/58, 82/90, 98/106, 114/122, 130/138, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298 and 306/282. In one embodiment, the HCVR/LCVR amino acid sequence pair is selected from the group consisting

of SEQ ID NOs:18/26, 66/74 and 146/154.

[0050] In a related embodiment, the description features a composition, which is a combination of at least two antibodies of the description and a pharmaceutically acceptable carrier or diluent.

[0051] In a related embodiment, the description features a composition, which is a combination/cocktail of at least three antibodies of the description and a pharmaceutically acceptable carrier or diluent.

[0052] In one embodiment, the pharmaceutical composition comprises (a) a first anti-Ebola virus antibody, comprising an HCVR/LCVR amino acid sequence pair as described in Table 1, or an antigen-binding fragment thereof; (b) a second anti-Ebola virus antibody, comprising an HCVR/LCVR amino acid sequence pair as described in Table 1, or antigen-binding fragment thereof; and (c) a third anti-Ebola virus antibody, comprising an HCVR/LCVR amino acid sequence pair as described in Table 1, or antigen-binding fragment thereof, wherein the first antibody binds to, or interacts with, a first epitope on Ebola virus GP and the second and/or third antibody binds to, or interact(s) with a different epitope on Ebola virus GP, and (d) a pharmaceutically acceptable carrier or diluent.

[0053] In another related embodiment, the description features a composition, which is a combination of an anti-Ebola virus GP antibody and a second therapeutic agent.

[0054] In one embodiment, the second therapeutic agent is any agent that is advantageously combined with an anti-Ebola virus GP antibody. Exemplary agents that may be advantageously combined with an anti-Ebola virus antibody include, without limitation, other agents that bind and/or inhibit Ebola virus activity (including other antibodies or antigen-binding fragments thereof, etc.) and/or agents, which do not directly bind Ebola virus but nonetheless inhibit viral activity including infectivity of host cells.

[0055] In certain embodiments, the description includes for a pharmaceutical composition comprising: (a) a first anti-Ebola virus antibody comprising an HCVR/LCVR amino acid sequence pair as described in Table 1, or antigen-binding fragment thereof; (b) a second anti-Ebola virus antibody comprising an HCVR/LCVR amino acid sequence pair as described in Table 1, or antigen-binding fragment thereof, wherein the first antibody binds to a first epitope on Ebola virus GP and the second antibody binds to a second epitope on Ebola virus GP wherein the first and second epitopes are distinct and non-overlapping; and (c) a pharmaceutically acceptable carrier or diluent.

[0056] In certain embodiments, the description includes for a pharmaceutical composition comprising: (a) a first anti-Ebola virus antibody or antigen-binding fragment thereof; (b) a second anti-Ebola virus antibody or antigen-binding fragment thereof, wherein the first antibody does not cross-compete with the second antibody for binding to Ebola virus; and (c) a pharmaceutically acceptable carrier or diluent.

[0057] In certain embodiments, the description includes for a pharmaceutical composition comprising: (a) a first anti-Ebola virus antibody or antigen-binding fragment thereof; (b) a

second anti-Ebola virus antibody or antigen-binding fragment thereof, which interacts with a different Ebola virus antigen, wherein the first antibody binds to an epitope on Ebola virus GP and the second antibody binds to an epitope on a different Ebola virus antigen; and (c) a pharmaceutically acceptable carrier or diluent.

[0058] In certain embodiments, the description includes for a pharmaceutical composition comprising: (a) a first anti-Ebola virus antibody or antigen-binding fragment thereof; (b) a second anti-Ebola virus antibody or antigen-binding fragment thereof; (c) a third anti-Ebola virus antibody or antigen-binding fragment thereof, wherein the first antibody binds to a first epitope on Ebola virus GP and the second and/or third antibody binds to a different epitope on Ebola virus GP wherein the first, second and third epitopes are distinct and non-overlapping; and (d) a pharmaceutically acceptable carrier or diluent.

[0059] In certain embodiments, the description includes for a pharmaceutical composition comprising: (a) a first anti-Ebola virus antibody or antigen-binding fragment thereof; (b) a second anti-Ebola virus antibody or antigen-binding fragment thereof; (c) a third anti-Ebola virus antibody or an antigen-binding fragment thereof, wherein the first antibody may or may not cross-compete with the second, and/or third antibody for binding to Ebola virus; and (d) a pharmaceutically acceptable carrier or diluent.

[0060] In certain embodiments, the description includes for a pharmaceutical composition comprising: (a) a first anti-Ebola virus antibody or antigen-binding fragment thereof; (b) a second and/or third anti-Ebola virus antibody or antigen-binding fragment thereof, which interacts with a different Ebola virus antigen, wherein the first antibody binds to an epitope on Ebola virus and the second and/or third antibody binds to an epitope on a different Ebola virus antigen; and (c) a pharmaceutically acceptable carrier or diluent.

[0061] In one embodiment, the pharmaceutical composition comprises a first anti-Ebola virus antibody or an antigen-binding fragment thereof that binds to, or interacts with one epitope on one strain of Ebola virus and the second and/or third anti-Ebola virus antibody or an antigen-binding fragment thereof that binds to, or interacts with a second and/or a third epitope on the same strain or on a different strain of Ebola virus. The Ebola virus strains that interact with an antibody of the description may be selected from the group consisting of the Zaire.2014, Zaire.1995, Sudan, Bundibugyo, and Cote d'Ivoire strains, or variants thereof.

[0062] In a related embodiment, the description includes a pharmaceutical composition comprising a first isolated monoclonal antibody or an antigen-binding fragment thereof that binds specifically to Ebola virus GP, wherein the first isolated monoclonal antibody or an antigen-binding fragment thereof comprises an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30 and an LCDR3 amino acid sequence of SEQ ID NO: 32, and a pharmaceutically acceptable carrier or diluent. The pharmaceutical composition may further

comprise a second isolated monoclonal antibody or an antigen-binding fragment thereof that binds specifically to Ebola virus GP, wherein the second isolated monoclonal antibody or an antigen-binding fragment thereof comprises an HCDR1 amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 70; an HCDR3 amino acid sequence of SEQ ID NO: 72; an LCDR1 amino acid sequence of SEQ ID NO: 76; an LCDR2 amino acid sequence of SEQ ID NO: 78 and an LCDR3 amino acid sequence of SEQ ID NO: 80. The pharmaceutical composition may further comprise a third isolated monoclonal antibody or an antigen-binding fragment thereof that binds specifically to Ebola virus GP, wherein the third isolated monoclonal antibody or an antigen-binding fragment thereof comprises an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158 and an LCDR3 amino acid sequence of SEQ ID NO: 160.

[0063] In certain embodiments, each antibody may be formulated as a separate formulation and if it is determined that more than one antibody is needed to achieve maximal therapeutic efficacy, each of the antibody formulations may be co-administered (concurrently, or sequentially), as needed. Alternatively, the antibody cocktail may be co-formulated.

[0064] In certain embodiments, when two or more antibodies are combined together in one pharmaceutical composition, they may or may not bind the same or overlapping epitopes on the Ebola virus protein. Additional combination therapies and co-formulations involving the anti-Ebola virus antibodies of the present description are disclosed elsewhere herein.

[0065] Also described are therapeutic methods for treating a disease or disorder associated with Ebola virus (such as viral infection in a subject), or at least one symptom associated with the viral infection, or the frequency or severity of at least one symptom associated with EBOV infection, using an anti-Ebola virus GP antibody or antigen-binding portion of an antibody of the description, or a cocktail of at least two or more antibodies of the description, wherein the therapeutic methods comprise administering a therapeutically effective amount of at least two or more antibodies or antigen-binding fragments of the description to the subject in need thereof. In one embodiment, the methods comprise administering a combination (cocktail) of at least three antibodies of the description. In one embodiment, the antibody cocktail comprises three anti-EBOV antibodies having the amino acid sequence pairs as set forth in SEQ ID NOs: 18/26, 66/74 and 146/154. The disorder treated is any disease or condition, which is improved, ameliorated, inhibited or prevented by inhibition of Ebola virus activity. In certain embodiments, the description includes methods to prevent, treat or ameliorate at least one symptom of Ebola virus infection, the method comprising administering a therapeutically effective amount of at least one or more anti-Ebola virus GP antibodies or antigen-binding fragments thereof of the description to a subject in need thereof.

[0066] In a related embodiment, the description includes a method of neutralizing infectious

EBOV, the method comprising exposing a cell infected with EBOV to a composition comprising one or more anti-EBOV antibodies or antigen-binding fragments thereof, wherein the exposing results in enhanced protection of the cell from virus infection, or from cell death. In certain embodiments, the exposing may be *in vitro* or *in vivo*. In one embodiment, the methods comprise administering one or more antibodies of the description. In one embodiment, the methods comprise administering a combination (cocktail) of at least three antibodies of the description. In one embodiment, the antibody cocktail comprises three anti-EBOV antibodies having the amino acid sequence pairs as set forth in SEQ ID NOs: 18/26, 66/74 and 146/154.

[0067] In some embodiments, the present description includes methods to ameliorate or reduce the severity, duration, or frequency of occurrence, of at least one symptom of Ebola virus infection in a subject by administering one or more anti-Ebola virus GP antibodies of the description, wherein the at least one symptom is selected from the group consisting of fever, headache, fatigue, loss of appetite, myalgia, diarrhea, vomiting, abdominal pain, dehydration and unexplained bleeding.

[0068] In certain embodiments, the description includes methods to decrease viral load in a subject, the methods comprising administering to the subject an effective amount of one or more antibodies or fragments thereof of the description that binds Ebola virus GP and blocks Ebola virus binding and/or entry into the host cell.

[0069] In a related embodiment, the description includes a method of increasing the survival, or the likelihood of survival of a subject suffering from infection with EBOV, or a subject exposed to EBOV, or at risk for exposure to, or for acquiring EBOV, the method comprising administering at least one antibody or antigen-binding fragment of the description, or a pharmaceutical composition comprising at least one antibody of the description to a subject in need thereof.

[0070] In one embodiment, the description includes a method of increasing the survival, or the likelihood of survival of a subject suffering from infection with EBOV, or a subject exposed to EBOV, or at risk for exposure to, or for acquiring EBOV, the method comprising administering an antibody cocktail comprising a mixture of at least two anti-EBOV antibodies of the description. In one embodiment, the method comprises administering an antibody cocktail comprising a mixture of at least three anti-EBOV antibodies of the description. In one embodiment, the antibody cocktail to be administered comprises a mixture of at least three anti-EBOV antibodies of the description, wherein the at least three antibodies comprise HCVR/LCVR amino acid sequence pairs as set forth in SEQ ID NOs: 18/26, 66/74 and 146/154.

[0071] In one embodiment, the subject in need thereof is a subject at risk for exposure to, or for acquiring an Ebola virus infection, wherein the subject is selected from the group consisting of an immunocompromised individual, a healthcare worker, a person who is suspected of having been exposed to a person harboring the Ebola virus, a person who comes into physical contact or close physical proximity with an infected individual, a hospital employee, a pharmaceutical researcher, maintenance personnel responsible for cleaning a hospital facility or institution

where an Ebola patient has been treated, individuals who have visited or are planning to visit an area or country known to have or suspected to have an outbreak of Ebola virus and a frequent flyer.

[0072] In one embodiment, the subject in need thereof may be administered at least one anti-EBOV antibody of the description or an antigen-binding fragment thereof, or a pharmaceutical composition comprising at least one antibody or antigen-binding fragment thereof of the description in combination with a second therapeutic agent. The second therapeutic agent may be selected from the group consisting of an anti-viral drug, an anti-inflammatory drug (such as corticosteroids, and non-steroidal anti-inflammatory drugs), a different antibody to EBOV, a vaccine for EBOV, TKM Ebola (small interfering RNAs that target viral RNA polymerase) brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537 (antisense phosphorodiamidate morpholino oligomers that target Ebola virus VP24 gene) and interferons.

[0073] In one embodiment, the pharmaceutical composition may be administered subcutaneously, intravenously, intradermally, intramuscularly, intranasally, or orally.

[0074] In a related embodiment, enhanced protection may be observed in a mammal exposed to, or infected with EBOV when the mammal is treated with a pharmaceutical composition comprising an antibody cocktail, which comprises at least three antibodies of the description.

[0075] In one embodiment, the enhanced protection observed may be measured by a decrease in the severity or frequency of at least one symptom associated with EBOV infection, by a decrease in viral load, or by an increase in survival of a mammal infected with EBOV. The at least one symptom may be selected from the group consisting of fever, headache, fatigue, loss of appetite, myalgia, diarrhea, vomiting, abdominal pain, dehydration and unexplained bleeding.

[0076] The enhanced protection may be observed when the antibody is used alone, or when it is used in combination with one or more additional therapeutic agents or anti-EBOV treatment modalities.

[0077] The one or more additional therapeutic agents may be selected from the group consisting of an anti-viral drug, an anti-inflammatory drug (such as corticosteroids, and non-steroidal anti-inflammatory drugs), a different antibody to Ebola virus, a vaccine for Ebola virus, TKM Ebola (small interfering RNAs that target viral RNA polymerase) brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537 (antisense phosphorodiamidate morpholino oligomers that target Ebola virus VP24 gene) and interferons.

[0078] In one embodiment, the one or more additional therapeutic agents comprise one or more anti-EBOV antibodies.

[0079] In one embodiment, the one or more anti-EBOV antibodies comprise a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

[0080] In a related embodiment, the one or more anti-EBOV antibodies comprise a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence pair

selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298 and 306/282.

[0081] In another related embodiment, the one or more anti-EBOV antibodies comprise a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26, 66/74 and 146/154.

[0082] In certain embodiments, the one or more antibodies or antigen-binding fragments thereof may be administered prophylactically or therapeutically to a subject having, or at risk of having, or pre-disposed to developing an Ebola virus infection. The subjects at risk include, but are not limited to, an immunocompromised person, for example, a person who is immunocompromised because of autoimmune disease, or those persons receiving immunosuppressive therapy (for example, following organ transplant), or those persons afflicted with human immunodeficiency syndrome (HIV) or acquired immune deficiency syndrome (AIDS), certain forms of anemia that deplete or destroy white blood cells, those persons receiving radiation or chemotherapy, or those persons afflicted with an inflammatory disorder. Other subjects at risk for acquiring an Ebola virus infection include healthcare workers, or any person who comes into physical contact or close physical proximity with an infected individual, or is exposed to bodily fluids or tissues from infected individuals, also has an increased risk of developing an Ebola virus infection. Moreover, a subject is at risk of contracting an Ebola virus infection due to proximity to an outbreak of the disease, e.g. a subject resides in a densely-populated city or in close proximity to subjects having confirmed or suspected Ebola virus infections, or choice of employment, e.g. maintenance personnel responsible for cleaning a hospital facility or institution where an Ebola patient has been treated, a hospital employee, a pharmaceutical researcher, an individual who has visited or who is planning to visit an area or country known to have or suspected to have an outbreak of Ebola virus, or a frequent flyer.

[0083] In certain embodiments, the antibody or antigen-binding fragment thereof of the description is administered in combination with a second therapeutic agent to the subject in need thereof. The second therapeutic agent may be selected from the group consisting of an anti-inflammatory drug (such as corticosteroids, and non-steroidal anti-inflammatory drugs), an anti-infective drug, an anti-viral drug, a different antibody to Ebola virus, a vaccine for Ebola virus, TKM Ebola (small interfering RNAs that target viral RNA polymerase) brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537 (antisense phosphorodiamidate morpholino oligomers that target Ebola virus VP24 gene), interferons, a dietary supplement such as anti-oxidants and any other drug or therapy known in the art useful for ameliorating at least one symptom of the Ebola virus infection, or for reducing the viral load in a patient. In certain embodiments, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with an antibody or antigen-binding fragment thereof of the description, if such side effect(s) should occur. The antibody or fragment thereof may be

administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intranasally, intramuscularly, or intracranially. In one embodiment, the antibody may be administered as a single intravenous infusion for maximum concentration of the antibody in the serum of the subject. The antibody or fragment thereof may be administered at a dose of about 0.1 mg/kg of body weight to about 100 mg/kg of body weight of the subject. In certain embodiments, an antibody of the present description may be administered at one or more doses comprising between 50mg to 600mg.

[0084] The present description also includes an anti-Ebola virus antibody or antigen-binding fragment thereof of the description for use in treating a subject who has, or is suspected of having, or has been exposed to EBOV, or for use in the manufacture of a medicament for the treatment of a disease or disorder that would benefit from the blockade of Ebola virus binding and/or activity.

[0085] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0086] Figure 1: H1H17161P potently neutralizes live EBOV.

[0087] Figure 2: Shows the interaction of three Anti-EBOV Antibodies with Ebola GP or Ebola soluble GP (sGP).

DETAILED DESCRIPTION

[0088] 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.

[0089] 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

[0089A] The term “comprising” as used in this specification and claims means “consisting at least in part of”. When interpreting statements in this specification, and claims which include the term “comprising”, it is to be understood that other features that are additional to the features prefaced by this term in each statement or claim may also be present. Related terms such as “comprise” and “comprised” are to be interpreted in similar manner.

[0090] “Ebola virus” or “EBOV” is a genus of the *Filoviridae* family, which is known to cause severe and rapidly progressing hemorrhagic fever. There are many different Ebola virus species and strains based on nucleotide sequence and outbreak location, for example, Zaire, Tai Forest

(previously known as Cote d'Ivoire or Ivory Coast), Sudan, Reston, and Bundibugyo. The most lethal forms of the virus are the Zaire and Sudan strains. The Reston strain is the only strain known to infect only non-human primates. The term "Ebola virus" also includes variants of Ebola virus isolated from different Ebola virus isolates.

[0091] The amino acid sequence of full-length Ebola virus glycoprotein, noted herein as "EBOV GP" or "Ebola virus GP" is exemplified by the amino acid sequences found in GenBank as accession numbers AHX24649.1 (See also SEQ ID NO: 314) and AHX24649.2 (See also SEQ ID NO: 315). The term also encompasses Ebola virus GP or a fragment thereof coupled to, for example, a histidine tag (*e.g.* see accession number AHX24649.1 with a decahistidine tag (SEQ ID NO: 318)), mouse or human Fc, or a signal sequence. The amino acid sequence of the "soluble GP" or "sGP" is shown in accession number AHX24650 and as SEQ ID NO 316 (with a signal sequence) and also SEQ ID NO: 317 (without the signal sequence but with a myc-myc-hexahistidine tag). The amino acid sequence of "GP1" starts at the amino terminal end of full length GP at residue 1 and ends at residue 501 of SEQ ID NO: 315. The amino acid sequence of "GP2" spans residues 502 through 676 of full length GP shown as SEQ ID NO: 315.

[0092] The term "Ebola virus infection", or "EBOV infection", as used herein refers to the severe hemorrhagic fever resulting from exposure to the virus, or to an infected animal, or to an infected human patient, or contact with the bodily fluids or tissues from an animal or human patient having an Ebola virus infection. The "symptoms associated with an Ebola virus infection" include fever, headache, fatigue, loss of appetite, myalgia, diarrhea, vomiting, abdominal pain, dehydration and unexplained bleeding.

[0093] 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 description, 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.

[0094] 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).

[0095] 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.

[0096] The fully human anti-Ebola virus 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 description 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 description 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 description.

[0097] The present description also includes fully human anti-Ebola virus 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 description includes anti-Ebola virus 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.

[0098] 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 description 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. The term includes antibodies recombinantly produced in a non-human mammal, or in cells of a non-human mammal. The term is not intended to include antibodies isolated from or generated in a human subject.

[0099] The term “recombinant”, as used herein, refers to antibodies or antigen-binding fragments thereof of the description created, expressed, isolated or obtained by technologies or methods known in the art as recombinant DNA technology which include, *e.g.*, DNA splicing and transgenic expression. The term refers to antibodies expressed in a non-human mammal (including transgenic non-human mammals, *e.g.*, transgenic mice), or a cell (*e.g.*, CHO cells) expression system or isolated from a recombinant combinatorial human antibody library.

[0100] 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 $1x10^{-7}$ 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 Ebola virus. Moreover, multi-specific antibodies that bind to one domain in Ebola virus and one or more additional antigens or a bi-specific that binds to

two different regions of Ebola virus are nonetheless considered antibodies that "specifically bind", as used herein.

[0101] The term "high affinity" antibody refers to those mAbs having a binding affinity to Ebola virus, expressed as K_D, of at least 10^{-7} M; preferably 10^{-8} M; more preferably 10^{-9}M, even 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.

[0102] By the term "slow off rate", "Koff" or "kd" is meant an antibody that dissociates from Ebola virus, or a virus like particle expressing the Ebola virus GP, with a rate constant of 1 x 10^{-3} s^{-1} or less, preferably 1 x 10^{-4} s^{-1} or less, as determined by surface plasmon resonance, *e.g.*, BIACORE™.

[0103] 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 fragment" 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 Ebola virus.

[0104] In specific embodiments, antibody or antibody fragments of the description may be conjugated to a moiety such a ligand or a therapeutic moiety ("immunoconjugate"), such as an anti-viral drug, a second anti-Ebola virus antibody, or any other therapeutic moiety useful for treating an infection caused by Ebola virus.

[0105] 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 Ebola virus, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than Ebola virus.

[0106] A "blocking antibody" or a "neutralizing antibody", as used herein (or an "antibody that neutralizes Ebola virus activity" or "antagonist antibody"), is intended to refer to an antibody whose binding to Ebola virus results in inhibition of at least one biological activity of Ebola virus. For example, an antibody of the description may prevent or block Ebola virus attachment to, or entry into a host cell. In addition, a "neutralizing antibody" is one that can neutralize, i.e., prevent, inhibit, reduce, impede or interfere with, the ability of a pathogen to initiate and/or perpetuate an infection in a host. The terms "neutralizing antibody" and "an antibody that neutralizes" or "antibodies that neutralize" are used interchangeably herein. These antibodies can be used, alone or in combination, as prophylactic or therapeutic agents with other anti-viral agents upon appropriate formulation, or in association with active vaccination, or as a diagnostic tool.

[0107] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" is a mechanism of cell-mediated immune defense whereby an effector cell of the immune system actively lyses a target cell, whose membrane-surface antigens have been bound by specific antibodies, such as by

those described herein. As such, it is one mechanism through which, for example, a virus specific antibody can act to limit the spread of infection. Classical ADCC is mediated by natural killer cells (NK cells), macrophages, neutrophils and in certain instances, eosinophils.

[0108] 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.).

[0109] The term "K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0110] 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.

[0111] The term “cross-competes”, as used herein, means an antibody or antigen-binding fragment thereof binds to an antigen and inhibits or blocks the binding of another antibody or antigen-binding fragment thereof. The term also includes competition between two antibodies in both orientations, *i.e.*, a first antibody that binds and blocks binding of second antibody and vice-versa. In certain embodiments, the first antibody and second antibody may bind to the same epitope. Alternatively, the first and second antibodies may bind to different, but overlapping epitopes such that binding of one inhibits or blocks the binding of the second antibody, *e.g.*, *via* steric hindrance. Cross-competition between antibodies may be measured by methods known in the art, for example, by a real-time, label-free bio-layer interferometry assay. To determine if a test antibody cross-competes with a reference anti-Ebola virus GP antibody of the description, the reference antibody is allowed to bind to an Ebola virus GP or peptide under saturating conditions. Next, the ability of a test antibody to bind to the Ebola virus GP is assessed. If the test antibody is able to bind to Ebola virus GP following saturation binding with the reference anti-Ebola virus GP antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-Ebola virus antibody. On the other hand, if the test antibody is not able to bind to the Ebola virus GP following saturation binding with the reference anti-Ebola virus GP antibody, then the test antibody may bind to the same epitope as the epitope bound by

the reference anti-Ebola virus GP antibody of the description.

[0112] 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.

[0113] 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.

[0114] 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 description 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. 25:3389-3402.

[0115] 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).

[0116] As used herein, the term "subject" refers to an animal, preferably a mammal, more preferably a human, in need of amelioration, prevention and/or treatment of a disease or disorder such as viral infection. The subject may have an Ebola virus infection or is predisposed to developing an Ebola virus infection. Subjects "predisposed to developing an Ebola virus infection", or subjects "who may be at elevated risk for contracting an Ebola virus infection", are those subjects with compromised immune systems because of autoimmune disease, those persons receiving immunosuppressive therapy (for example, following organ transplant), those persons afflicted with human immunodeficiency syndrome (HIV) or acquired immune deficiency syndrome (AIDS), certain forms of anemia that deplete or destroy white blood cells, those persons receiving radiation or chemotherapy, or those persons afflicted with an inflammatory disorder. Additionally, subjects of extreme young or old age are at increased risk. Any person who comes into physical contact or close physical proximity with an infected animal, or human patient, or is exposed to bodily fluids or tissues from an infected animal or human patient, has an increased risk of developing an Ebola virus infection. Moreover, a subject is at risk of contracting an Ebola virus infection due to proximity to an outbreak of the disease, e.g. subject resides in a densely-populated city or in close proximity to subjects having confirmed or suspected infections of Ebola virus, or choice of employment, e.g. hospital worker, pharmaceutical researcher, an individual who has visited or who is planning to visit an area or country known to have or suspected to have an outbreak of Ebola virus, or a frequent flyer.

[0117] As used herein, the terms "treat", "treating", or "treatment" refer to the reduction or amelioration of the severity of at least one symptom or indication of Ebola virus infection due to the administration of a therapeutic agent such as an antibody of the present description to a subject in need thereof. The terms include inhibition of progression of disease or of worsening of infection. The terms also include positive prognosis of disease, i.e., the subject may be free of

infection or may have reduced or no viral titers upon administration of a therapeutic agent such as an antibody of the present description. The therapeutic agent may be administered at a therapeutic dose to the subject.

[0118] The terms “prevent”, “preventing” or “prevention” refer to inhibition of manifestation of Ebola virus infection or any symptoms or indications of Ebola virus infection upon administration of an antibody of the present description. The term includes prevention of spread of infection in a subject exposed to the virus or at risk of having Ebola virus infection.

[0119] As used herein, the term “anti-viral drug” refers to any anti-infective agent or therapy, whether it be a chemical moiety, or a biological therapy, used to treat, prevent, or ameliorate a viral infection in a subject. For example, in the present description an anti-viral drug may include, but not be limited to, an antibody to Ebola virus (in one embodiment the antibody to Ebola virus may be different than those described herein), a vaccine for Ebola virus, TKM Ebola (small interfering RNAs that target viral RNA polymerase) brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537 (antisense phosphorodiamidate morpholino oligomers that target Ebola virus VP24 gene) and interferons. In the present description, the infection to be treated is caused by an Ebola virus.

General Description

[0120] Ebola virus disease is a severe, often fatal disease caused by filamentous viral particles that are members of the family *Filoviridae*. There are several known species of the genus Ebola virus that are capable of causing disease in humans. These include Zaire, Sudan, Tai Forest (formerly Ivory Coast) and Bundibugyo. The natural reservoir for the virus is unknown and to date there are no approved therapies or vaccines.

[0121] The genome of the virus consists of a single strand of negative sense RNA of approximately 19 kb in length. Ebola virions contain seven proteins: a surface glycoprotein (GP), a nucleoprotein (NP), four virion structural proteins (VP40, VP35, VP30, and VP24), and an RNA-dependent RNA polymerase (L). (Feldman, *et al*. (1992) Virus Res. 24, 1-19).

[0122] The only protein present on the surface of the virus is the glycoprotein. Due to RNA editing, the transcription of the GP gene results in the synthesis of several GP gene specific mRNAs coding for viral GPs including non-structural soluble GP (sGP) and surface virion GP (Volchkova, VA *et al*., (1998), Virology 250:408-414). Both GPs are synthesized as a precursor molecule that is proteolytically cleaved by the cellular protease furin during intracellular processing (Volchkov, VE, *et al.,* ((1998), Proc Natl Acad Sci USA 95:5762-5767). sGP forms dimers, whereas the cleaved carboxy-terminus fragment is a monomer. Viral surface spikes are formed as a trimer of $GP_{1,2}$ made up of two subunits GP1 and GP2 linked by a disulfide bond (Volchkova, VA *et al*., (1998), Virology 250:408-414; Falzarano, D. *et al.,* (2006), Chembiochem 7:1605-1611). GP1 is known to mediate viral attachment to the host cell and GP2 is involved in membrane fusion (Sanchez, A. et al., (1996), Proc Natl Acad Sci USA 93:3602-3607; Alazard-Dany, N*., et al.* (2006), J. Gen. Virol. 87:1247-1257).

[0123] During infection with EBOV, significant amounts of soluble glycoproteins (sGP) are released from virus-infected cells. This form of GP has been shown to bind to and sequester virus-neutralizing antibodies directed against surface or virion GP (Dolnik, O. *et al.,* (2004), EMBO J 23:2175-2184). Other than this antibody-blockade, the role of soluble GP in terms of viral replication and/or pathogenicity has not been well defined. More recent studies by Escudero-Perez, *et al.,* have shown that sGP may bind to and activate non-infected dendritic cells and macrophages and induce the secretion of pro- and anti-inflammatory cytokines. In addition, they demonstrated that sGP affects endothelial cell function and may affect vascular permeability. (Escudero-Perez, *et al*., (2014), PLOS Pathogens, Vol. 10, Issue 11:1-17). This may explain the dysregulated inflammatory host reaction following infection and may contribute to virus pathogenicity.

[0124] Passive immunotherapy for prophylaxis or treatment of infectious diseases has been used for more than a century, usually in the form of convalescent human sera that contains high titers of neutralizing antibodies (Good *et al*., (1991); Cancer 68: 1415-1421). Today, multiple purified monoclonal antibodies are currently in preclinical and clinical development for use as anti-microbials (Marasco et al 2007; Nature Biotechnology 25: 1421-1434). Certain antibodies have been described that bind to the Ebola virus glycoprotein. (See *e.g*. Audet *et. al.* (2014), Scientific Reports 4:6881; Chen, *et.al.* (2014), ACS Chem Biol. Oct. 17; 9(10):2263-73; Koellhoffer JF, *et.al.,* (2012), Chembiochem Nov. 26; 13(17):2549-57; Qiu, X., *et. al*., Nature (2014) Oct 2;514(7520):47-53).

[0125] The inventors have described herein fully human antibodies and antigen-binding fragments thereof that specifically bind to Ebola virus GP and modulate the interaction of Ebola virus with those cells. The anti-Ebola virus GP antibodies may bind to the Ebola virus with high affinity. In certain embodiments, the antibodies of the present description are blocking antibodies wherein the antibodies may bind to Ebola virus GP and block the attachment to and/or entry of the virus into host cells. In certain embodiments, the antibodies of the description may block the binding of Ebola virus to cells and as such may inhibit or neutralize viral infection of host cells. In certain embodiments, the antibodies of the description may mediate antibody dependent cell-mediated cytotoxicity (ADCC) and as such, may aid in destroying cells that harbor the virus. In certain embodiments, the antibodies may act in both fashions, *e.g.* they may neutralize viral infectivity and may mediate ADCC. In some embodiments, the antibodies may be useful for treating a subject suffering from an Ebola virus infection. The antibodies when administered to a subject in need thereof may reduce the infection by a virus such as Ebola virus in the subject. They may be used to decrease viral loads in a subject. They may be used alone or as adjunct therapy with other therapeutic moieties or modalities known in the art for treating a viral infection. In certain embodiments, these antibodies may bind to an epitope in the amino terminus of the Ebola virus GP. In certain embodiments, these antibodies may bind to an epitope in the carboxy terminus of the Ebola virus GP. Furthermore, the identified antibodies

can be used prophylactically (before infection) to protect a mammal from infection, or can be used therapeutically (after infection is established) to ameliorate a previously established infection, or to ameliorate at least one symptom associated with the infection.

[0126] The full-length amino acid sequence of an exemplary Ebola virus GP is shown in GenBank as accession numbers AHX24649.1 and AHX24649.2 and also in SEQ ID NOs: 314 and 315, respectively. GP1 spans from amino acid residue 1-501 of the full length GP and GP2 spans from amino acid residue 502 through 676 of the full length GP shown in SEQ ID NOs 314 or SEQ ID NO: 315). The full length EBOV GP, also shown in accession number AHX24649.1, may be coupled to a decahistidine tag, such as shown in SEQ ID NO: 318. Soluble GP (sGP) is shown as GenBank accession number AHX24650.1 and also as SEQ ID NO: 316 (with the signal sequence attached) and also as SEQ ID NO: 317 (without the signal sequence, but containing a myc-myc-his tag).

[0127] In certain embodiments, the antibodies of the description are obtained from mice immunized with a primary immunogen, such as a full-length Ebola virus GP, or with a recombinant form of Ebola virus GP or fragments thereof followed by immunization with a secondary immunogen, or with an immunogenically active fragment of Ebola virus GP. In certain embodiments, the antibodies are obtained from mice immunized with DNA encoding the full-length Ebola virus GP (Zaire.2014, see GenBank KJ660346.2; also SEQ ID NO: 313). The immunogen may be a biologically active and/or immunogenic fragment of Ebola virus GP or DNA encoding the active fragment thereof. The fragment may be derived from any region of the viral GP, including the amino-terminal fragment (*e.g.* GP1), or the carboxy-terminal fragment (*e.g.* GP2). 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.

[0128] Certain anti-Ebola virus antibodies of the present description are able to bind to and neutralize the activity of Ebola virus, as determined by *in vitro* or *in vivo* assays. The ability of the antibodies of the description to bind to and neutralize the activity of Ebola virus and thus the attachment and/or entry of the virus into a host cell followed by the ensuing viral infection, may be measured using any standard method known to those skilled in the art, including binding assays, or activity assays, as described herein.

[0129] Non-limiting, exemplary *in vitro* assays for measuring binding activity are illustrated in Example 3, herein. In Example 3, the binding affinity and dissociation constants of anti-Ebola virus GP antibodies for Ebola virus were determined by Biacore. In Examples 4 and 7, neutralization assays were used to determine infectivity of diverse strains of Ebola virus.

[0130] The antibodies specific for Ebola virus GP 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. In one embodiment, the label may be a radionuclide, a fluorescent dye or a MRI-detectable label. In certain embodiments, such labeled antibodies may be used in diagnostic assays including imaging assays.

Antigen-Binding Fragments of Antibodies

[0131] 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 fragment" 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 Ebola virus. 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. In certain embodiments, the term "antigen-binding fragment" refers to a polypeptide fragment of a multi-specific antigen-binding molecule. 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.

[0132] 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.

[0133] 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.

[0134] 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 description 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 description 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)).

[0135] 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 description using routine techniques available in the art.

Preparation of Human Antibodies

[0136] 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 description to make human antibodies that specifically bind to Ebola virus GP. An immunogen comprising any one of the

following can be used to generate antibodies to Ebola virus. In certain embodiments, the antibodies of the description are obtained from mice immunized with a full-length, native Ebola virus GP (See, for example, GenBank accession numbers AHX24649.1 (SEQ ID NO: 314) and AHX24649.2 (SEQ ID NO: 315) or with DNA encoding the glycoprotein or fragment thereof. Alternatively, the Ebola virus GP or a fragment thereof may be produced using standard biochemical techniques and modified and used as immunogen. In one embodiment, the immunogen is a recombinantly produced Ebola virus GP or fragment thereof. In certain embodiments of the description, the immunogen may be a commercially available Ebola virus GP. In certain embodiments, one or more booster injections may be administered. In certain embodiments, the booster injections may comprise one or more commercially available Ebola virus GPs. In certain embodiments, the immunogen may be a recombinant Ebola virus GP expressed in *E. coli* or in any other eukaryotic or mammalian cells such as Chinese hamster ovary (CHO) cells.

[0137] 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 Ebola virus GP 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.

[0138] 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.

[0139] 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 description, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

[0140] The anti-Ebola virus GP antibodies and antibody fragments of the present description encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind Ebola virus. 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 description 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 description.

[0141] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single dose or multiple doses. 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.

[0142] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, or potency.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] Bioequivalent variants of the antibodies of the description 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.

Anti-Ebola virus Antibodies Comprising Fc Variants

[0147] According to certain embodiments of the present description, anti-Ebola virus antibodies are described comprising an Fc domain comprising one or more mutations that enhance or diminish antibody binding to the FcRn receptor, *e.g.*, at acidic pH as compared to neutral pH. For example, the present description includes anti-Ebola virus GP antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.,* in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (*e.g.,* A, W, H, F or Y [N434A, N434W, N434H, N434F or N434Y]); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (*e.g.,* 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (*e.g.,* M428L) and 434S (*e.g.,* N434S) modification; a 428L, 259I (*e.g.,* V259I), and 308F (*e.g.,* V308F) modification; a 433K (*e.g.,* H433K) and a 434 (*e.g.,* 434Y) modification; a 252, 254, and 256 (*e.g.,* 252Y, 254T, and 256E) modification; a 250Q and 428L modification (*e.g.,* T250Q and M428L); and a 307 and/or 308 modification (*e.g.,* 308F or 308P). In yet another embodiment, the modification comprises a 265A (*e.g.*, D265A) and/or a 297A (*e.g.*, N297A) modification.

[0148] For example, the present description includes anti-Ebola virus antibodies comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (*e.g.*, T250Q and M248L); 252Y, 254T and 256E (*e.g.*, M252Y, S254T and T256E); 428L and 434S (*e.g.*, M428L and N434S); 257I and 311I (*e.g.*, P257I and

Q311I); 257I and 434H (*e.g.*, P257I and N434H); 376V and 434H (*e.g.*, D376V and N434H); 307A, 380A and 434A (*e.g.*, T307A, E380A and N434A); and 433K and 434F (*e.g.*, H433K and N434F). All possible combinations of the foregoing Fc domain mutations and other mutations within the antibody variable domains disclosed herein are contemplated within the present description.

[0149] The present description also includes anti-Ebola virus antibodies comprising a chimeric heavy chain constant (C_H) region, wherein the chimeric C_H region comprises segments derived from the C_H regions of more than one immunoglobulin isotype. For example, the antibodies of the description may comprise a chimeric C_H region comprising part or all of a C_H2 domain derived from a human IgG1, human IgG2 or human IgG4 molecule, combined with part or all of a C_H3 domain derived from a human IgG1, human IgG2 or human IgG4 molecule. According to certain embodiments, the antibodies of the description comprise a chimeric C_H region having a chimeric hinge region. For example, a chimeric hinge may comprise an "upper hinge" amino acid sequence (amino acid residues from positions 216 to 227 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a "lower hinge" sequence (amino acid residues from positions 228 to 236 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. According to certain embodiments, the chimeric hinge region comprises amino acid residues derived from a human IgG1 or a human IgG4 upper hinge and amino acid residues derived from a human IgG2 lower hinge. An antibody comprising a chimeric C_H region as described herein may, in certain embodiments, exhibit modified Fc effector functions without adversely affecting the therapeutic or pharmacokinetic properties of the antibody. (*See*, *e.g.*, U.S. Provisional Appl. No. 61/759,578, filed February 1, 2013).

Biological Characteristics of the Antibodies

[0150] In general, the antibodies of the present description function by binding to Ebola virus GP. For example, the present description includes antibodies and antigen-binding fragments of antibodies that bind Ebola virus GP (*e.g.*, at 25ºC or at 37ºC) with a K_D of less than 10^{-7}M, as measured by surface plasmon resonance, *e.g.,* using the assay format as described herein. In certain embodiments, the antibodies or antigen-binding fragments thereof bind Ebola virus GP with a K_D of less than about 10nM, less than about 5nM, less than about 1nM, less than about 500pM, less than 250pM, or less than 100pM, as measured by surface plasmon resonance, e.g., using the assay format as described herein, or a substantially similar assay.

[0151] The present description also includes antibodies and antigen-binding fragments thereof that bind Ebola virus with a dissociative half-life (t½) of greater than about 3 minutes as measured by surface plasmon resonance at 25ºC, or greater than about 1 minute as measured by surface plasmon resonance at 37ºC *e.g.*, and at least a 3-fold increase in dissociative half-life

(t½) at pH 5 or pH 6; using an assay format as defined herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present description bind Ebola virus with a t½ of greater than about 10 minutes, of greater than about 30 minutes, of greater than about 60 minutes, of greater than about 100 minutes, of greater than about 200 minutes, greater than about 300 minutes, greater than about 400 minutes, greater than about 500 minutes, greater than about 600 minutes, greater than about 700 minutes, greater than about 800 minutes, greater than about 900 minutes, or greater than about 1000 minutes as measured by surface plasmon resonance at 25ºC, or at 37ºC *e.g.*, using an assay format as defined herein (*e.g.*, mAb-capture or antigen-capture format), or a substantially similar assay.

[0152] The present description also includes antibodies or antigen-binding fragments thereof that neutralize the infectivity of Ebola virus for its host cells. In some embodiments, the antibodies exhibit a neutralization potency against Zaire.2014 VLPs with an IC_{50} ranging from about 10^{-11} M to about 10^{-9} M. The antibodies of the description also cross react with Ebola virus VLPs containing GPs from various strains of EBOV, including Zaire.1995, Zaire.2014, Ebola Sudan, Bundibugyo and Cote d'Ivoire (Ivory Coast). The antibodies of the description also mediate ADCC as shown in Example 5. Furthermore, the antibodies of the description cross-compete with other antibodies that bind EBOV GP, as shown in Example 6.

[0153] In one embodiment, the description includes an isolated recombinant antibody or antigen-binding fragment thereof that binds specifically to Ebola virus GP, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (a) is a fully human monoclonal antibody; (b) binds to EBOV, or a virus like particle (VLP) expressing an Ebola virus glycoprotein with a dissociation constant (K_D) of less than 10^{-7}M, as measured in a surface plasmon resonance assay; (c) demonstrates at least a 3 fold increase in dissociative half-life (t½) at pH 5 or pH 6 relative to pH 7.4; (d) demonstrates neutralization of Zaire Ebola virus with an IC_{50} ranging from about 10^{-11} M to about 10^{-9} M; (e) demonstrates antibody dependent cellular cytotoxicity of Ebola virus infected cells; (f) cross reacts with one or more strains of Ebola virus VLPs selected from the group consisting of Zaire.2014, Zaire.1995, Sudan, Bundibugyo and Cote d'Ivoire; (g) cross-competes with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

[0154] The antibodies of the present description may possess one or more of the aforementioned biological characteristics, or any combinations thereof. Certain of the properties of the antibodies of the description are summarized below. Other biological characteristics of the antibodies of the present description will be evident to a person of ordinary skill in the art from a review of the present disclosure including the working Examples herein.

mAb	mAb Properties	Pseudovirus neutralization	Live Virus Neutralization	ADCC	sGP Binding

		IC50 (M)			
H1H17161P	Neutralizer, ADCC-, sGP-	8.3E-11	Yes	No	No
H1H17139P	Non Neutralizer, ADCC +, sGP+	No	No	Yes	Yes
H1H17203P	Neutralizer, ADCC +, sGP-	2E-10	No	Yes	No

Epitope Mapping and Related Technologies

[0155] The present description includes anti-Ebola virus antibodies that interact with one or more amino acids found within the GP of Ebola virus. The epitope to which the antibodies bind may consist of a single contiguous sequence of 3 or more (*e.g.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids located within the Ebola virus GP molecule (*e.g.* a linear epitope in a domain). Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) located within the Ebola virus GP (*e.g.* a conformational epitope).

[0156] 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, routine cross-blocking assays, such as that described in Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harbor, NY). 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) Prot. Sci. 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: 252-259; Engen and Smith (2001) Anal. Chem. 73: 256A-265A.

[0157] 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.

[0158] 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 (see 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 description into groups of antibodies binding different epitopes.

[0159] In certain embodiments, the Ebola virus antibodies or antigen-binding fragments thereof bind an epitope within any one or more of the regions exemplified in Ebola virus GP, either in natural form, or recombinantly produced, or to a fragment thereof.

[0160] The present description includes anti-Ebola virus GP antibodies that bind to the same epitope, or a portion of the epitope. Likewise, the present description also includes anti-Ebola virus GP antibodies that compete for binding to Ebola virus GP or a fragment thereof with any of the specific exemplary antibodies described herein. For example, the present description includes anti-Ebola virus GPP antibodies that cross-compete for binding to Ebola virus with one or more antibodies obtained from those antibodies described in Tables 1 and 2.

[0161] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-Ebola virus GP 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-Ebola virus GP antibody of the description, the reference antibody is allowed to bind to a Ebola virus GP or peptide under saturating conditions. Next, the ability of a test antibody to bind to the Ebola virus GP is assessed. If the test antibody is able to bind to Ebola virus GP following saturation binding with the reference anti-Ebola virus GP antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-Ebola virus antibody. On the other hand, if the test antibody is not able to bind to the Ebola virus GP following saturation binding with the reference anti-Ebola virus GP antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-Ebola virus GP antibody of the description.

[0162] To determine if an antibody competes for binding with a reference anti-Ebola virus GP antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a Ebola virus GP under saturating conditions followed by assessment of binding of the test antibody to the Ebola virus GP. In a second orientation, the test antibody is allowed to bind to an Ebola virus GP under saturating

conditions followed by assessment of binding of the reference antibody to the Ebola virus GP. If, in both orientations, only the first (saturating) antibody is capable of binding to the Ebola virus GP, then it is concluded that the test antibody and the reference antibody compete for binding to Ebola virus GP. 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.

[0163] 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.

[0164] 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

[0165] The description encompasses a human anti-Ebola virus GP monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an anti-viral drug to treat Ebola virus infection. As used herein, the term "immunoconjugate" refers to an antibody, which is chemically or biologically linked to a radioactive agent, a cytokine, an interferon, a target or reporter moiety, an enzyme, a peptide or protein or a therapeutic agent. The antibody may be linked to the radioactive agent, cytokine, interferon, target or reporter moiety, enzyme, peptide or therapeutic agent at any location along the molecule so long as it is able to bind its target. Examples of immunoconjugates include antibody drug conjugates and antibody-toxin fusion proteins. In one embodiment, the agent may be a second different antibody to Ebola virus, or Ebola virus GP. In certain embodiments, the antibody may be conjugated to an agent specific for a virally infected cell. The type of therapeutic moiety that may be conjugated to the anti-Ebola virus antibody and will take into account the condition to be treated and the desired therapeutic effect to be achieved. Examples of suitable agents for forming immunoconjugates are known in the art; see for example, WO 05/103081.

Multi-specific Antibodies

[0166] The antibodies of the present description 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.

[0167] Any of the multi-specific antigen-binding molecules of the description, or variants thereof, may be constructed using standard molecular biological techniques (e.g., recombinant DNA and protein expression technology), as will be known to a person of ordinary skill in the art.

[0168] In some embodiments, Ebola virus-specific antibodies are generated in a bi-specific format (a "bi-specific") in which variable regions binding to distinct domains of Ebola virus are linked together to confer dual-domain specificity within a single binding molecule. Appropriately designed bi-specifics may enhance overall Ebola virus-protein inhibitory efficacy through increasing both specificity and binding avidity. Variable regions with specificity for individual domains, (*e.g*., segments of the N-terminal domain), 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).

[0169] Alternatively, antibodies that bind more than one domain and a second target, such as, but not limited to, for example, a second different anti-Ebola virus antibody, 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 regions may be linked together with variable regions that bind to relevant sites on, for example, Ebola virus, to confer dual-antigen specificity within a single binding molecule. Appropriately designed bi-specifics of this nature serve a dual function. Variable regions with specificity for the extracellular domain are combined with a variable region with specificity for outside the extracellular domain and are paired on a structural scaffold that allows each variable region to bind to the separate antigens.

[0170] An exemplary bi-specific antibody format that can be used in the context of the present description 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 description.

[0171] Other exemplary bispecific formats that can be used in the context of the present description include, without limitation, *e.g.*, scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (*e.g.*, common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED)body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab^2 bispecific formats (*see*, *e.g.*, Klein *et al.* 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, *e.g.*, wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (*See*, *e.g.*, Kazane *et al.*, *J. Am. Chem. Soc.* [*Epub*: *Dec. 4, 2012*]).

Therapeutic Administration and Formulations

[0172] The description includes therapeutic compositions comprising the anti-Ebola virus GP antibodies or antigen-binding fragments thereof of the present description. Therapeutic compositions in accordance with the description 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.

[0173] The dose of antibody may vary depending upon the age and the size of a subject to be

administered, target disease, conditions, route of administration, and the like. When an antibody of the present description is used for treating a disease or disorder in an adult patient, or for preventing such a disease, it is advantageous to administer the antibody of the present description normally at a single dose of about 0.1 to about 60 mg/kg body weight, more preferably about 5 to about 60, about 10 to about 50, or about 20 to about 50 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. In certain embodiments, the antibody or antigen-binding fragment thereof of the description can be administered as an initial dose of at least about 0.1 mg to about 800 mg, about 1 to about 500 mg, about 5 to about 300 mg, or about 10 to about 200 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 antibody or antigen-binding fragment 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.

[0174] Various delivery systems are known and can be used to administer the pharmaceutical composition of the description, *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. The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see, for example, Langer (1990) Science 249:1527-1533).

[0175] The use of nanoparticles to deliver the antibodies of the present description is also contemplated herein. Antibody-conjugated nanoparticles may be used both for therapeutic and diagnostic applications. Antibody-conjugated nanoparticles and methods of preparation and use are described in detail by Arruebo, M., et al. 2009 ("Antibody-conjugated nanoparticles for biomedical applications" in J. Nanomat. Volume 2009, Article ID 439389, 24 pages, doi: 10.1155/2009/439389). Nanoparticles may be developed and conjugated to antibodies contained in pharmaceutical compositions to target virally infected cells. Nanoparticles for drug delivery have also been described in, for example, US 8257740, or US 8246995.

[0176] 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.

[0177] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous, intracranial, intraperitoneal 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.

[0178] A pharmaceutical composition of the present description 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 description. 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.

[0179] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present description. 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 description 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, Thousand Oaks, CA), the PENLET ™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.) and the HUMIRA ™ Pen (Abbott Labs, Abbott Park, IL), to name only a few.

[0180] 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 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 antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Therapeutic Uses of the Antibodies

[0181] The antibodies of the present description are useful for the treatment, and/or prevention of a disease or disorder or condition associated with Ebola virus infection and/or for ameliorating at least one symptom associated with such disease, disorder or condition.

[0182] In certain embodiments, the antibodies of the description are useful to treat subjects suffering from the severe and acute respiratory infection caused by Ebola virus. In some embodiments, the antibodies of the description are useful in decreasing viral titers or reducing viral load in the host. In one embodiment, an antibody or antigen-binding fragment thereof the description may be administered at a therapeutic dose to a patient with Ebola virus infection.

[0183] One or more antibodies of the present description may be administered to relieve or prevent or decrease the severity of one or more of the symptoms or conditions of the disease or disorder. The antibodies may be used to ameliorate or reduce the severity of at least one symptom of Ebola virus infection including, but not limited to fever, headache, fatigue, loss of appetite, myalgia, diarrhea, vomiting, abdominal pain, dehydration and unexplained bleeding.

[0184] It is also contemplated herein to use one or more antibodies of the present description prophylactically to subjects at risk for developing an Ebola virus infection such as an immunocompromised individual, a healthcare worker, a person who is suspected of having been exposed to a person harboring the Ebola virus, a person who comes into physical contact or close physical proximity with an infected individual, a hospital employee, a pharmaceutical researcher, maintenance personnel responsible for cleaning a hospital facility or institution where an Ebola patient has been treated, individuals who have visited or are planning to visit an area or country known to have or suspected to have an outbreak of Ebola virus or a frequent flyer.

[0185] In a further embodiment of the description the present antibodies are used for the preparation of a pharmaceutical composition for treating patients suffering from an Ebola virus infection. In another embodiment of the description, the present antibodies are used as adjunct therapy with any other agent or any other therapy known to those skilled in the art useful for treating or ameliorating an Ebola virus infection.

Combination Therapies

[0186] Combination therapies may include an anti-Ebola virus GP antibody of the description and any additional therapeutic agent that may be advantageo usly combined with an antibody of the description, or with a biologically active fragment of an antibody of the description. The antibodies of the present description may be combined synergistically with one or more drugs or agents used to treat Ebola virus infection.

[0187] For example, exemplary agents for treating a viral infection may include, *e.g.,* anti-viral drug, an anti-inflammatory drug (such as corticosteroids, and non-steroidal anti-inflammatory drugs), a different antibody to Ebola virus, a vaccine for Ebola virus, TKM Ebola (small interfering RNAs that target viral RNA polymerase) brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537 (antisense phosphorodiamidate morpholino oligomers that target Ebola virus VP24 gene), interferons, or any other palliative therapy to treat an Ebola virus infection.

[0188] In some embodiments, the antibodies of the description may be combined with a second therapeutic agent to reduce the viral load in a patient with an Ebola virus infection, or to ameliorate one or more symptoms of the infection.

[0189] In certain embodiments, the second therapeutic agent is another different antibody, or antibody cocktail specific for Ebola virus GP, wherein the different antibody or antibodies within the cocktail may or may not bind to the same epitope, or an overlapping epitope, as an antibody of the present description. In certain embodiments, the second therapeutic agent is an antibody to a different Ebola virus protein. The second antibody may be specific for one or more different Ebola virus proteins from different strains of the virus. It is contemplated herein to use a combination ("cocktail") of the antibodies of the description with neutralization or inhibitory activity against Ebola virus. In some embodiments, non-competing antibodies may be combined and administered to a subject in need thereof, to reduce the ability of Ebola virus to escape due to mutation. In some embodiments, the antibodies comprising the combination bind to distinct non-overlapping epitopes on the GP. The antibodies comprising the combination may block the virus attachment and/or entry into and/or fusion with host cells. The antibodies may interact with the GP from a strain of EBOV selected from Zaire, Sudan, Bundibugyo, or Cote d'Ivoire, and when used alone, or in combination with any one or more of the agents noted above, may neutralize any one or more of the Ebola virus strains noted.

[0190] It is also contemplated herein to use a combination of anti-Ebola virus GP antibodies of the present description, wherein the combination comprises one or more antibodies that do not cross-compete. In certain embodiments, the combination includes a cocktail comprising a mixture of at least three antibodies of the description. The antibodies within the cocktail may differ in their ability to neutralize virus or virus infected cells, or in their ability to mediate antibody-dependent cellular cytotoxicity (ADCC), or in their ability to bind EBOV soluble glycoprotein (sGP).

[0191] As used herein, the term “in combination with” means that additional therapeutically active component(s) may be administered prior to, concurrent with, or after the administration of at least one anti-Ebola virus GP antibody of the description, or a cocktail comprising one or more of the antibodies the present description. The term “in combination with” also includes sequential or concomitant administration of an anti-Ebola virus GP antibody and a second therapeutic agent.

[0192] The additional therapeutically active component(s) may be administered to a subject prior to administration of an anti-Ebola virus GP antibody of the present description. For example, a first component may be deemed to be administered "prior to" a second component if the first component is administered 1 week before, 72 hours before, 60 hours before, 48 hours before, 36 hours before, 24 hours before, 12 hours before, 6 hours before, 5 hours before, 4 hours before, 3 hours before, 2 hours before, 1 hour before, 30 minutes before, 15 minutes before, 10 minutes before, 5 minutes before, or less than 1 minute before administration of the second component. In other embodiments, the additional therapeutically active component(s) may be administered to a subject after administration of an anti-Ebola virus GP antibody of the present description. For example, a first component may be deemed to be administered "after" a second component if the first component is administered 1 minute after, 5 minutes after, 10 minutes after, 15 minutes after, 30 minutes after, 1 hour after, 2 hours after, 3 hours after, 4 hours after, 5 hours after, 6 hours after, 12 hours after, 24 hours after, 36 hours after, 48 hours after, 60 hours after, 72 hours after administration of the second component. In yet other embodiments, the additional therapeutically active component(s) may be administered to a subject concurrent with administration of an anti-Ebola virus GP antibody of the present description. "Concurrent" administration, for purposes of the present description, includes, *e.g.*, administration of an anti-Ebola virus GP antibody and an additional therapeutically active component to a subject in a single dosage form, or in separate dosage forms administered to the subject within about 30 minutes or less of each other. If administered in separate dosage forms, each dosage form may be administered via the same route (*e.g.*, both the anti-Ebola virus GP antibody and the additional therapeutically active component may be administered intravenously, etc.); alternatively, each dosage form may be administered via a different route (*e.g.*, the anti-Ebola virus GP antibody may be administered intravenously, and the additional therapeutically active component may be administered orally). In any event, administering the components in a single dosage from, in separate dosage forms by the same route, or in separate dosage forms by different routes are all considered "concurrent administration," for purposes of the present disclosure. For purposes of the present disclosure, administration of an anti-Ebola virus GP antibody "prior to", "concurrent with," or "after" (as those terms are defined herein above) administration of an additional therapeutically active component is considered administration of an anti-Ebola virus GP antibody "in combination with" an additional therapeutically active component.

[0193] The present description includes pharmaceutical compositions in which an anti- Ebola virus GP antibody of the present description is co-formulated with one or more of the additional therapeutically active component(s) as described elsewhere herein.

Administration Regimens

[0194] According to certain embodiments, a single dose of an anti-Ebola virus GP antibody of the description (or a pharmaceutical composition comprising a combination of an anti-Ebola virus GP antibody and any of the additional therapeutically active agents mentioned herein) may be administered to a subject in need thereof. According to certain embodiments of the present description, multiple doses of an anti-Ebola virus GP antibody (or a pharmaceutical composition comprising a combination of an anti-Ebola virus GP antibody and any of the additional therapeutically active agents mentioned herein) may be administered to a subject over a defined time course. The methods according to this embodiment of the description comprise sequentially administering to a subject multiple doses of an anti-Ebola virus GP antibody of the description. As used herein, "sequentially administering" means that each dose of anti-Ebola virus GP antibody 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 description includes methods which comprise sequentially administering to the patient a single initial dose of an anti-Ebola virus GP antibody, followed by one or more secondary doses of the anti-Ebola virus GP antibody, and optionally followed by one or more tertiary doses of the anti-Ebola virus GP antibody.

[0195] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the anti-Ebola virus GP antibody of the description. 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 anti-Ebola virus GP antibody, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of anti-Ebola virus GP antibody contained in the initial, secondary and/or tertiary doses varies 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").

[0196] In certain exemplary embodiments of the present description, each secondary and/or tertiary dose is administered 1 to 48 hours (*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)

after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of anti-Ebola virus GP antibody, which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0197] The methods according to this embodiment of the description may comprise administering to a patient any number of secondary and/or tertiary doses of an anti-Ebola virus GP antibody. 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.

[0198] In certain embodiments of the description, 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.

Diagnostic Uses of the Antibodies

[0199] The anti-Ebola virus GP antibodies of the present description may be used to detect and/or measure Ebola virus in a sample, *e.g.*, for diagnostic purposes. Some embodiments contemplate the use of one or more antibodies of the present description in assays to detect a disease or disorder such as viral infection. Exemplary diagnostic assays for Ebola virus may comprise, *e.g.*, contacting a sample, obtained from a patient, with an anti-Ebola virus GP antibody of the description, wherein the anti-Ebola virus GP antibody is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate Ebola virus from patient samples. Alternatively, an unlabeled anti-Ebola virus GP 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 Ebola virus in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0200] Samples that can be used in Ebola virus diagnostic assays according to the present description include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of either Ebola virus, or fragments thereof, under normal or pathological conditions. Generally, levels of Ebola virus in a particular sample obtained from a healthy patient (*e.g.*, a patient not afflicted with a disease associated with Ebola virus will be measured to initially establish a baseline, or standard, level of Ebola virus. This baseline level of Ebola

virus can then be compared against the levels of Ebola virus measured in samples obtained from individuals suspected of having a Ebola virus -associated condition, or symptoms associated with such condition.

[0201] The antibodies specific for Ebola virus 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.

[0201A] In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

[0201B] Certain statements that appear herein are broader than what appears in the statements of the invention. These statements are provided in the interests of providing the reader with a better understanding of the invention and its practice. The reader is directed to the accompanying claim set which defines the scope of the invention.

EXAMPLES

[0202] 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, room temperature is about 25°C, and pressure is at or near atmospheric.

Example 1: Generation of Human Antibodies to Ebola virus

[0203] Human antibodies to Ebola virus were generated in a mouse comprising DNA encoding human immunoglobulin heavy and kappa light chain variable regions. In one embodiment, the human antibodies to Ebola virus were generated in a VELOCIMMUNE® mouse. In one embodiment, VelocImmune® (VI) mice were immunized with DNA encoding the full-length Ebola virus GP [Zaire ebolavirus 2014 (GenBank: KJ660346.2)]. Antibodies were generated following an accelerated regimen comprising 2 immunizations separated by 2 weeks. The antibody immune response was monitored by an Ebola virus GP-specific immunoassay. For

example, sera were assayed for specific antibody titers to purified full-length EBOV GP, subunit GP proteins (GP1 and GP2), and virus-like particles (VLPs) expressing EBOV GP. Antibody-producing clones were isolated using both B-cell Sorting Technology (BST) and hybridoma methods. For example, 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 Ebola virus GP-specific antibodies. Using this technique, and the various immunogens described above, several chimeric antibodies (*i.e.*, antibodies possessing human variable domains and mouse constant domains) were obtained; exemplary antibodies generated in this manner were designated as H1M17354N, H2aM17356N, H1M17357N, H2aM17358N, H2aM17359N and H2aM17360N.

[0204] Anti-Ebola virus antibodies were also isolated directly from antigen-positive mouse B cells without fusion to myeloma cells, as described in U.S. Patent 7582298. Using this method, several fully human anti-Ebola virus GP antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as H1H17134P, H1H17139P, H1H17142P, H1H17151P, H1H17161P, H1H17162P, H1H17193P, H1H17196P, H1H17199P, H1H17203P, H1H17214P, H1H17219P, H1H17223P and H1H17228P.

[0205] 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 and Nucleotide Sequences

[0206] Table 1 sets forth the amino acid sequence identifiers of the heavy and light chain variable regions and CDRs of selected anti-Ebola virus antibodies of the description. The corresponding nucleic acid sequence identifiers are set forth in Table 2.

Table 1: Amino Acid Sequence Identifiers

	SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
H1H17134P	2	4	6	8	10	12	14	16
H1H17139P	18	20	22	24	26	28	30	32
H1H17142P	34	36	38	40	42	44	46	48
H1H17151P	50	52	54	56	58	60	62	64
H1H17161P	66	68	70	72	74	76	78	80
H1H17162P	82	84	86	88	90	92	94	96
H1H17193P	98	100	102	104	106	108	110	112
H1H17196P	114	116	118	120	122	124	126	128
H1H17199P	130	132	134	136	138	140	142	144
H1H17203P	146	148	150	152	154	156	158	160
H1H17214P	162	164	166	168	170	172	174	176

H1H17219P	178	180	182	184	186	188	190	192
H1H17223P	194	196	198	200	202	204	206	208
H1H17228P	210	212	214	216	218	220	222	224
H1H17354N	226	228	230	232	234	236	238	240
H1H17356N	242	244	246	248	250	252	254	256
H1H17357N	258	260	262	264	266	268	270	272
H1H17358N2	274	276	278	280	282	284	286	288
H1H17359N	290	292	294	296	298	300	302	304
H1H17360N	306	308	310	312	282	284	286	288
H1M17354N	226	228	230	232	234	236	238	240
H2aM17356N	242	244	246	248	250	252	254	256
H1M17357N	258	260	262	264	266	268	270	272
H2aM17358N	274	276	278	280	282	284	286	288
H2aM17359N	290	292	294	296	298	300	302	304
H2aM17360N	306	308	310	312	282	284	286	288

Table 2: Nucleic Acid Sequence Identifiers

	SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
H1H17134P	1	3	5	7	9	11	13	15
H1H17139P	17	19	21	23	25	27	29	31
H1H17142P	33	35	37	39	41	43	45	47
H1H17151P	49	51	53	55	57	59	61	63
H1H17161P	65	67	69	71	73	75	77	79
H1H17162P	81	83	85	87	89	91	93	95
H1H17193P	97	99	101	103	105	107	109	111
H1H17196P	113	115	117	119	121	123	125	127
H1H17199P	129	131	133	135	137	139	141	143
H1H17203P	145	147	149	151	153	155	157	159
H1H17214P	161	163	165	167	169	171	173	175
H1H17219P	177	179	181	183	185	187	189	191
H1H17223P	193	195	197	199	201	203	205	207
H1H17228P	209	211	213	215	217	219	221	223
H1H17354N	225	227	229	231	233	235	237	239
H1H17356N	241	243	245	247	249	251	253	255
H1H17357N	257	259	261	263	265	267	269	271
H1H17358N2	273	275	277	279	281	283	285	287
H1H17359N	289	291	293	295	297	299	301	303
H1H17360N	305	307	309	311	281	283	285	287
H1M17354N	225	227	229	231	233	235	237	239
H2aM17356N	241	243	245	247	249	251	253	255
H1M17357N	257	259	261	263	265	267	269	271
H2aM17358N	273	275	277	279	281	283	285	287
H2aM17359N	289	291	293	295	297	299	301	303
H2aM17360N	305	307	309	311	281	283	285	287

[0207] Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (*e.g.* "H1H," "H2M," etc.), followed by a numerical identifier (*e.g.* "17139," "17161," etc., as shown in Table 1 or 2), followed by a "P," "P2," "N", N2, or "B" suffix. The H1H and H2M prefixes on the antibody designations used herein indicate the particular Fc region isotype of the

antibody. Thus, according to this nomenclature, an antibody may be referred to herein as, *e.g.*, "H1H17359N," "H2aM17359N," etc. For example, an "H1M" antibody has a mouse IgG1 Fc, and an "H2M" antibody has a mouse IgG2 Fc (a or b isotype) (all variable regions are fully human as denoted by the first 'H' in the antibody designation). As will be appreciated by a person of ordinary skill in the art, an antibody having a particular Fc isotype can be converted to an antibody with a different Fc isotype (*e.g.*, an antibody with a mouse IgG1 Fc can be converted to an antibody with a human IgG4, etc.), but in any event, the variable domains (including the CDRs) – which are indicated by the numerical identifiers shown in Table 1 or 2 – will remain the same, and the binding properties to antigen are expected to be identical or substantially similar regardless of the nature of the Fc domain.

Example 3: Antibody binding to Ebola virus GP as determined by Surface Plasmon Resonance

A. pH Dependent dissociation rate constant at 37°C

[0208] Binding dissociation rate constants (k_d) and dissociation half-lives ($t_{½}$) for Ebola virus GP binding to purified anti-Ebola virus GP monoclonal antibodies at 37° C were determined using a real-time surface plasmon resonance biosensor assay on a Biacore T200 instrument. The CM4 Biacore sensor surface was derivatized by amine coupling with a monoclonal mouse anti-human Fc antibody (GE, # BR-1008-39) or monoclonal goat anti-mouse Fc antibody (GE, # BR-1008-38) to capture purified anti-Ebola virus GP mAbs. All Biacore binding studies in Example 3A were performed in a buffer composed of 0.01M Na_2HPO_4/NaH_2PO_4, 0.15M NaCl, 0.05% v/v Surfactant P20 (PBS-P running buffer) at pHs 7.4, 6.0 and 5.0. The low pH chase was performed to assess whether the antibodies maintain binding at low pH. This would mimic the conditions that the virus will encounter during membrane fusion, upon acidification of the endosome. Different concentrations of Ebola virus GP with a C-terminal polyhistidine tag (EbolaGP.his; Sino Biologicals, Catalog # 40442-V08B1) prepared in PBS-P running buffer (ranging from 90 nM to 11.1 nM, 3-fold dilutions) were injected over the anti-Ebola virus GP mAb captured surface at a flow rate of 25µL/minute. Association of Ebola virus GP to the captured monoclonal antibody was monitored for 5 minutes and the dissociation of Ebola virus GP in PBS-P running buffer was monitored for 6 minutes. All of the dissociation rate constant experiments were performed at 37°C. Kinetic dissociation (k_d) rate constants were determined by fitting the real-time sensorgrams to a 1:1 binding model using Scrubber 2.0c curve fitting software. The dissociative half-lives (t½) were calculated from the kinetic rate constants as:

$$t½ \text{ (min)} = \frac{\ln(2)}{60 \times kd}$$

[0209] Dissociation rate parameters for Ebola virus GP binding to purified anti-Ebola virus GP mAbs at 37°C are shown in Table 3.

Table 3: pH dependence of dissociative half-lives at 37°C

	t½ Ratio	
mAb Captured	**pH7.4 / pH6.0**	**pH7.4 / pH5.0**
H1H1238N(-) control	NB	NB
H1H17162P	0.3	0.3
H1H17177P	0.2	0.2
H1H17193P	1.1	0.8
H1H17196P	1.0	1.0
H1H17150P	0.2	0.2
H1H17151P	0.03	0.01
H1H17160P	0.2	0.4
H1H17161P	0.2	0.2
H1H17214P	1.0	1.0
H1H17219P	1.0	1.0
H1H17223P	0.4	0.4
H1H17228P	0.6	0.5
H1H17142P	0.5	0.5
H1H17141P	0.3	0.3
H1H17139P	0.2	0.2
H1H17134P	0.6	0.6
H1H17211P	6.7	3.0
H1H17210P	0.2	0.2
H1H17203P	0.2	0.1
H1H17199P	0.4	0.1
H1M17348N	0.3	0.4
H1M17349N	2.7	6.9
H1M17350N	0.1	1.1
H1M17351N	NB	NB
H1M17352N	1.1	1.1
H1M17353N	1.6	0.3
H1M17354N	1.3	1.3
H1M17357N	0.8	0.5
H2aM17355N	0.5	0.6
H2aM17356N	0.9	0.9
H2aM17358N	0.7	0.4
H2aM17359N	0.8	0.7
H2aM17360N	0.2	0.5
H2aM17361N	0.2	0.5

NB-No detectable binding under assays conditions tested

B. Binding Affinity and Kinetics at 25°C and 37°C

[0210] Equilibrium dissociation constants (K_D values) for Ebola virus GP binding to purified anti-Ebola virus GP mAbs were determined using a real-time surface plasmon resonance biosensor

using a Biacore 4000 instrument. The CM4 Biacore sensor surface was derivatized by amine coupling with a monoclonal mouse anti-human Fc antibody (GE, # BR-1008-39) or monoclonal goat anti-mouse Fc antibody (GE, # BR-1008-38) to capture purified anti-Ebola virus GP mAbs. All Biacore binding studies in Example 3B were performed in a buffer composed of 0.01M HEPES pH 7.4, 0.15M NaCl, 3mM EDTA, 0.05% v/v Surfactant P20 (HBS-ET running buffer). Different concentrations of Ebola virus GP with a C-terminal polyhistidine tag (Sino Biologicals, Catalog # 40442-V08B1) prepared in HBS-ET running buffer (ranging from 90 nM to 3.3 nM, 3-fold dilutions) were injected over the anti-Ebola virus GP mAb captured surface at a flow rate of 30μL/minute. Association of Ebola virus GP to the captured monoclonal antibody was monitored for 5 minutes and the dissociation of Ebola virus GP in HBS-ET running buffer was monitored for 10 minutes. All of the binding kinetics experiments were performed at 25°C and 37°C. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by fitting the real-time sensorgrams to a 1:1 binding model using Scrubber 2.0c curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives (t½) were calculated from the kinetic rate constants as:

$$K_D\ (M) = \frac{kd}{ka}, \quad \text{and} \quad t½\ (min) = \frac{\ln(2)}{60 \times kd}$$

[0211] Binding kinetic parameters for Ebola virus GP binding to purified anti-Ebola virus GP mAbs at 25°C and 37°C are shown in Tables 4A and 4B.

Table 4A: Binding Kinetics at 25°C

mAb	ka (1/Ms)	kd (1/s)	KD (M)	t1/2 (min)
H1H17162P	2.18E+04	≤ 1E-5	4.60E-10	≥ 1155
H1H17177P	3.18E+03	1.12E-05	3.53E-09	1030.3
H1H17193P	4.58E+03	1.08E-04	2.36E-08	106.6
H1H17196P	2.56E+04	≤ 1E-5	3.91E-10	≥ 1155
H1H17150P	2.16E+04	5.42E-05	2.51E-09	213.1
H1H17151P	1.26E+04	9.44E-05	7.49E-09	122.3
H1H17160P	6.85E+04	3.76E-03	5.48E-08	3.1
H1H17161P	5.29E+04	≤ 1E-5	1.89E-10	≥ 1155
H1H17214P	3.76E+04	≤ 1E-5	2.66E-10	≥ 1155
H1H17219P	3.11E+04	2.90E-05	9.34E-10	398.3
H1H17223P	3.00E+04	6.08E-05	2.03E-09	190.0
H1H17228P	4.49E+04	1.69E-03	3.76E-08	6.9
H1H17142P	2.00E+04	2.81E-05	1.41E-09	410.7
H1H17141P	1.98E+04	9.69E-05	4.90E-09	119.2
H1H17139P	2.29E+04	1.63E-04	7.13E-09	70.8
H1H17134P	7.65E+04	9.41E-04	1.23E-08	12.3
H1H17211P	3.33E+04	2.14E-04	6.43E-09	54.0
H1H17210P	1.09E+02	2.06E-04	1.89E-06	56.0
H1H17203P	2.78E+04	1.68E-04	6.04E-09	68.7

H1H17199P	1.25E+04	2.36E-04	1.89E-08	49.0
H1M17348N	IC	IC	IC	IC
H1M17349N	7.03E+04	8.69E-04	1.24E-08	13.3
H1M17350N	IC	IC	IC	IC
H1M17351N	NB	NB	NB	NB
H1M17352N	IC	IC	IC	IC
H1M17353N	IC	IC	IC	IC
H1M17354N	4.94E+04	3.16E-03	6.39E-08	3.7
H1M17357N	IC	IC	IC	IC
H2aM17355N	1.44E+04	≤ 1E-5	6.96E-10	≥ 1155
H2aM17356N	2.18E+04	9.57E-05	4.40E-09	120.7
H2aM17358N	3.22E+02	2.01E-04	6.23E-07	57.5
H2aM17359N	3.82E+03	1.95E-04	5.09E-08	59.4
H2aM17360N	2.30E+04	1.06E-05	4.63E-10	1086.5
H2aM17361N	1.22E+02	1.25E-04	1.02E-06	92.5

NB-No detectable binding under assays conditions tested

IC-Inconclusive binding sensogram for fitting

Table 4B Binding Kinetics at 37°C.

mAb	ka (1/Ms)	kd (1/s)	KD (M)	t1/2 (min)
H1H17162P	3.47E+04	≤ 1E-5	2.88E-10	≥ 1155
H1H17177P	1.68E+04	1.62E-04	9.62E-09	71.3
H1H17193P	1.58E+04	5.03E-04	3.18E-08	22.9
H1H17196P	3.16E+04	≤ 1E-5	3.17E-10	≥ 1155
H1H17150P	3.18E+04	3.94E-05	1.24E-09	292.8
H1H17151P	2.26E+04	3.83E-04	1.70E-08	30.2
H1H17160P	5.72E+04	5.63E-03	9.85E-08	2.1
H1H17161P	4.39E+04	≤ 1E-5	2.28E-10	≥ 1155
H1H17214P	3.67E+04	1.54E-04	4.20E-09	74.9
H1H17219P	4.41E+04	≤ 1E-5	2.27E-10	≥ 1155
H1H17223P	3.51E+04	2.42E-04	6.89E-09	47.7
H1H17228P	7.32E+04	3.83E-03	5.23E-08	3
H1H17142P	2.60E+04	1.74E-04	6.68E-09	66.6
H1H17141P	2.65E+04	2.92E-04	1.10E-08	39.6
H1H17139P	2.48E+04	5.12E-04	2.06E-08	22.5
H1H17134P	6.99E+04	4.69E-04	6.70E-09	24.6
H1H17211P	1.90E+04	7.31E-04	3.84E-08	15.8
H1H17210P	6.19E+02	6.12E-04	9.89E-07	18.9
H1H17203P	3.85E+04	1.19E-03	3.09E-08	9.7
H1H17199P	3.04E+04	1.28E-03	4.22E-08	9
H1M17348N	IC	IC	IC	IC
H1M17349N	1.77E+04	1.93E-03	1.09E-07	6
H1M17350N	4.84E+02	1.00E-03	2.07E-06	11.5
H1M17351N	NB	NB	NB	NB

H1M17352N	4.09E+04	1.55E-03	3.80E-08	7.4
H1M17353N	2.33E+02	5.38E-04	2.31E-06	21.5
H1M17354N	5.08E+04	5.73E-03	1.13E-07	2
H1M17357N	2.35E+04	1.84E-03	7.81E-08	6.3
H2aM17355N	1.99E+04	2.06E-04	1.03E-08	56.2
H2aM17356N	7.26E+03	2.50E-04	3.44E-08	46.2
H2aM17358N	1.07E+04	5.67E-04	5.28E-08	20.4
H2aM17359N	1.54E+04	3.52E-04	2.29E-08	32.8
H2aM17360N	2.43E+04	3.37E-04	1.39E-08	34.3
H2aM17361N	1.83E+04	4.15E-04	2.27E-08	27.8

NB-No detectable binding under assays conditions tested

IC-Inconclusive binding sensogram for fitting

Results

[0212] As shown in Tables 4A and 4B above, the antibodies bound to Ebola Virus GP with K_D values ranging from 934pM to 1890nM at 25°C and from 227pM to 2310nM at 37°C. At pH 7.4, the antibodies showed dissociative half-life (t½) values ranging from 3.0 minutes to greater than 1155 minutes at 25°C and from 2.0 minutes to greater than 1155 minutes at 37°C. No loss in binding was observed at low pH. Several antibodies showed increased dissociative half-life (t½) values at low pH relative to pH 7.4. Antibodies with 3-fold or greater increases in dissociative half-life (t½) values at pH 5 and/or pH 6 include H1H17162P, H1H17177P, H1H17150P, H1H17151P, H1H17160P, H1H17161P, H1H17141P, H1H17139P, H1H17210P, H1H17203P, H1H17199P, H1M17348N, H1M17350N, H2aM17360N and H2aM17361N.

Example 4: Generation of Ebola virus Pseudoparticles and Neutralization Studies

[0213] Ebola virus pseudoparticles (also called virus like particles, or VLPs) were generated by co-transfecting 293T cells with a mix of plasmid constructs expressing Ebola virus GP, HIV gag-pol, and an HIV proviral vector encoding for firefly luciferase. Supernatants containing Ebola virus pseudoparticles were harvested at 48 hours post transfection, clarified using centrifugation, aliquoted and frozen at -80°C. Control pseudoparticles were generated by substituting the plasmid expressing Ebola virus GP with a plasmid encoding for Vesicular Stomatitis virus glycoprotein (VSVg).

Ebola Pseudoparticle-based neutralization assay

[0214] The pseudoparticles generated as described above were tested in neutralization assays. Specifically, dilutions of antibodies were incubated with Ebola virus pseudoparticles for 1h at room temperature. Huh7 cells are detached using 0.02M EDTA, washed and incubated with the antibody/ pseudoparticle mixtures for 72h. Infection efficiency was quantitated by luciferase detection with the BrightGlo® luciferase assay (Promega, San Luis Obispo, CA, USA) and read in a Victor® X3 plate reader (Perkin Elmer, Waltham, MA, USA) for light production.

Table 5: Zaire 2014 VLP Neutralization

AB ID	Corresponding Hybridoma Ab ID	Neutralizer of Zaire 2014 VLP	IC50 (M)
H1H17134P		-	-
H1H17139P		-	-
H1H17142P		+	1.59E-09
H1H17151P		+	1.51E-09
H1H17161P		+	2.55E-10
H1H17162P		+	2.86E-10
H1H17193P		-	-
H1H17196P		+	1.68E-09
H1H17199P		-	-
H1H17203P		+	8.68E-10
H1H17214P		+	8.99E-10
H1H17219P		+	6.95E-10
H1H17223P		+	1.58E-09
H1H17228P		+	3.26E-09
H1M17354N	H1M17354N	-	-
H2aM17356N	H2aM17356N	+	4.77E-09
H1M17357N	H1M17357N	-	-
H2aM17358N	H2aM17358N	+	4.68E-09
H2aM17359N	H2aM17359N	+	3.36E-09
H2aM17360N	H2aM17360N	+	3.75E-09

[0215] The data shown above in Table 5 show that 14 out of the 20 anti-Ebola virus antibodies of the present description, using the experimental design described herein, potently neutralize infectivity with an IC_{50} ranging from about 10^{-11} M to about 10^{-9} M.

Example 5: Antibody-dependent cell-mediated cytotoxicity (ADCC) by Anti-Ebola virus Antibodies

[0216] Antibody-dependent cell-mediated cytotoxicity (ADCC) was tested by the ability of the antibodies to signal via a CD16 based reporter system (Promega ADCC reporter bioassay core kit, San Luis Obispo, CA, USA). Ebola virus GP-expressing 293 cells were seeded. One day later, diluted antibodies produced in fuc^- cell lines (See US Patent No. 8409838) and effector cells (1.5:1 effector to target ratio) are added and incubated overnight. Reporter activity was measured with the BioGlo® luciferase assay (Promega, San Luis Obispo, CA, USA) and read in a Victor® X3 plate reader (Perkin Elmer, Waltham, MA, USA) for light production.

Table 6: ADCC Results

	ADCC Reporter Bioassay

Ab ID	Clone ID	ADCC Activity
H1H17134P		+
H1H17139P		+
H1H17142P		+
H1H17151P		+
H1H17161P		-
H1H17162P		-
H1H17193P		+
H1H17196P		+
H1H17199P		+
H1H17203P		+
H1H17214P		+
H1H17219P		-
H1H17223P		+
H1H17228P		+
H1M17354N	HCAF05C08-22	+
H2aM17356N	HCAF08C07-09	+
H1M17357N	HCAF09D11-13	+
H2aM17358N	HCAF12C05-14	+
H2aM17359N	HCAF12C06-26	+
H2aM17360N	HCAF12G09-07	+

[0217] The ability of the antibodies to mediate ADCC was calculated on the basis of activity compared to an isotype (negative) control. Any value greater than 5 fold above the negative control was considered positive. The data above in Table 6 show that 17 out of the 20 anti-Ebola virus antibodies mediated ADCC.

Example 6: Octet Cross-Competition

[0218] Binding competition between anti-Ebola virus GP monoclonal antibodies that had been previously determined to bind to Ebola virus GP was determined using a real time, label-free bio-layer interferometry (BLI) assay on an Octet HTX biosensor (ForteBio Corp., A Division of Pall Life Sciences). The binding of relevant controls for soluble GP (sGP), GP1, or GP2, was measured in the same assay format and its response was subtracted from the Ebola virus GP reagent of interest for each mAb tested. The entire experiment was performed at 25°C in buffer comprised of 0.01M HEPES pH7.4, 0.15M NaCl, 3mM EDTA, 0.05% v/v Surfactant P20, 1.0mg/mL BSA (Octet HBS-ET buffer) with the plate shaking at a speed of 1000rpm. To assess whether two antibodies are able to compete with one another for binding to their respective epitopes on the Ebola virus GP expressed with a C-terminal polyhistidine tag (Ebola virus GP.h, Sino Biologicals Inc., also see GenBank AHX24649.1 and SEQ ID NO: 314), approximately ~1.0nm of Ebola virus GP was first captured onto anti-penta-His antibody coated Octet

biosensors (Fortebio Inc, # 18-5079) by submerging the biosensors for 3 minutes into wells containing a 20µg/mL solution of Ebola virus GP. The antigen-captured biosensors were then saturated with the first anti-Ebola virus GP monoclonal antibody (subsequently referred to as mAb-1) by immersion into wells containing a 50µg/mL solution of mAb-1 for 5 minutes. The biosensors were then subsequently submerged into wells containing a 50µg/mL solution of a second anti-Ebola virus GP monoclonal antibody (subsequently referred to as mAb-2) for 3 minutes. All the biosensors were washed in Octet HBS-ET buffer in between each step of the experiment. The real-time binding response was monitored during the course of the experiment and the binding response at the end of every step was recorded. The response of mAb-2 binding to Ebola virus GP pre-complexed with mAb-1 was compared and competitive/non-competitive behavior of different anti-Ebola virus GP monoclonal antibodies were determined using a 50% inhibition threshold. Table 7 explicitly defines the relationships of antibodies competing in both directions, independent of the order of binding.

[0219] As shown in Table 7, the column on the left shows the mAb1 antibodies that are captured using the AHC Octet biosensors and the column on the right demonstrates the antibodies (mAb2) that cross-compete with the mAb1 antibody.

Table 7: Cross-competition of anti-Ebola virus GP antibodies for binding to Ebola virus GP

First mAb (mAb-1) Captured using AHC Octet Biosensors	mAb-2 Antibodies Shown to Compete with mAb-1
H1H17160P	H1H17160P, H1M17354N, H1M17357N, H1H17228P, H1H17203P
H1M17354N	H1H17160P, H1M17354N, H1M17357N, H1H17228P, H1H17203P
H1M17357N	H1H17160P, H1M17354N, H1M17357N, H1H17228P, H1H17203P
H1H17228P	H1H17160P, H1M17354N, H1M17357N, H1H17228P, H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N
H1H17203P	H1H17160P, H1M17354N, H1M17357N, H1H17228P, H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N
H1H17151P	H1H17228P, H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17353N, H1H17223P, H1H17196P, H1H17193P
H1H17142P	H1H17228P, H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N, H1M17353N, H1H17223P, H1H17196P, H1H17193P

H1H17177P	H1H17228P, H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N, H1H17141P, H1H17223P, H1H17196P, H1H17139P, H1H17193P, H1M17350N
H2aM17359N	H1H17228P, H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N H2aM17356N, H2aM17361N, H2aM17355N, 1H17211P, H1M17348N, H1M17353N, H1H17141P, H1H17223P H1H17139P, H1H17193P, H1M17350N
H1H17214P	H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N H1H17141P, H1H17223P, H1H17139P H1H17193P, H1M17350N
H1H17199P	H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N, H1H17141P, H1H17139P, H1H17193P, H1M17350N
H2aM17358N	H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N H1H17139P, H1H17193P, H1M17350N
H2aM17360N	H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N H1M17353N, H1H17139P, H1H17193P, H1M17350N
H1M17352N	H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N, H1H17139P, H1H17193P, H1M17350N
H2aM17356N	H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N H2aM17361N, H2aM17355N, H1H17211P, H1M17348N H1M17353N, H1H17139P, H1H17193P, H1M17350N
H2aM17361N	H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N, H1H17139P, H1H17193P, H1M17350N
H2aM17355N	H1H17203P, H1H17151P, H1H17142P, H1H17177P, H2aM17359N H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N H1M17353N, H1H17193P, H1M17350N
H1H17211P	H1H17151P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N H1H17193P, H1M17350N
H1M17348N	H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N H2aM17355N, H1H17211P, H1M17348N, H1M17353N, H1H17193P H1M17350N
H1M17353N	H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P H1H17199P, H2aM17358N, H2aM17360N, H1M17352N

	H2aM17356N, H2aM17361N, H2aM17355N, H1H17211P, H1M17348N, H1M17353N, H1H17141P, H1H17223P, H1H17196P, H1H17139P, H1H17193P
H1H17141P	H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H1M17353N H1H17141P, H1H17223P, H1H17196P, H1H17139P
H1H17223P	H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1M17353N H1H17141P, H1H17223P, H1H17196P, H1H17139P
H1H17196P	H1H17151P, H1H17142P, H1H17177P, H1M17353N, H1H17141P, H1H17223P, H1H17196P, H1H17139P
H1H17139P	H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H1M17353N H1H17141P, H1H17223P, H1H17196P, H1H17139P
H1H17193P	H1H17151P, H1H17142P, H1H17177P, H2aM17359N, H1H17214P, H1H17199P H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N H2aM17355N, H1H17211P, H1M17348N, H1M17353N, H1H17193P, H1M17350N
H1M17350N	H1H17177P, H2aM17359N, H1H17214P, H1H17199P, H2aM17358N, H2aM17360N, H1M17352N, H2aM17356N, H2aM17361N, H2aM17355N H1H17211P, H1M17348N, H1H17193P, H1M17350N
H1H17219P	H1H17219P, H1H17150P, H1H17161P
H1H17150P	H1H17219P, H1H17150P, H1H17161P
H1H17161P	H1H17219P, H1H17150P, H1H17161P
H1M17349N	H1M17349N
H1H17134P	H1H17134P
H1H17162P	H1H17162P
H1H17210P	H1H17210P

Example 7: Sequential Binding of H1H17203P, H1H17139P and H1H17161P to Ebola Virus Glycoprotein

[0220] Taking the information obtained from the cross-competition experiments, a sequential binding study was done to determine if three individual candidate antibodies are capable of binding simultaneously to soluble Ebola virus glycoprotein (GP), thereby confirming that the binding sites on Ebola virus GP are independent for each monoclonal antibody. If so, this information would support the use of these antibodies in a therapeutic cocktail.

[0221] Accordingly, sequential binding experiments, for three anti-Ebola virus GP monoclonal antibodies to Ebola virus GP, H1H17203P, H1H17139P and H1H17161P were tested for binding independently and non-competitively to Ebola virus GP. This experiment was done using a real time, label-free bio-layer interferometry (BLI) assay on an Octet RED biosensor (ForteBio Corp., A Division of Pall Life Sciences). The entire experiment was performed at 25°C in buffer comprised of 0.01M HEPES pH7.4, 0.15M NaCl, 3mM EDTA, 0.05% v/v Surfactant P20, 1.0mg/mL BSA (Octet HBS-ET buffer) with the plate shaking at a speed of 1000rpm. To assess whether three antibodies are able to bind simultaneously to captured antigen Ebola virus GP expressed with a C-terminal polyhistidine tag (Ebola virus GP.his, Sino Biologicals), approximately ~0.6nm of Ebola virus GP.h was first captured onto anti-penta-His antibody coated Octet biosensors (Fortebio Inc, # 18-5079) by submerging the biosensors for 3 minutes into wells containing a 20µg/mL solution of Ebola virus GP.h. The antigen-captured biosensors were then saturated with the first anti-Ebola virus GP monoclonal antibody (subsequently

referred to as H1H17161P) by immersion into wells containing a 50µg/mL solution of REGN H1H17161P for 5 minutes. The biosensors were then subsequently submerged into wells containing a 50µg/mL solution of a second anti-Ebola virus GP monoclonal antibody (subsequently referred to as H1H17139P) for 5 minutes. Finally, 50ug/mL of the third antibody (subsequently referred to as H1H17161P) was injected for 5 minutes to reach saturation. The real-time binding response was monitored during the course of the experiment and the binding response at the end of every step was recorded.

Results

[0222] The three candidate monoclonal antibodies tested were capable of binding simultaneously to Ebolavirus GP, indicating that each antibody did not interfere with the binding site on Ebolavirus GP of the other antibodies tested, suggesting that they each bound or interacted with different epitopes. This supports a role for use of these three antibodies in a therapeutic antibody cocktail.

Example 8: Binding of anti-Ebola Antibodies to Different Ebola Virus Like Particle (VLP) strains

[0223] A study was done to determine whether the anti-Ebola virus GP antibodies would react with virus like particles (VLPs) containing GPs from other Ebola virus strains. Included in this study were VLPs containing GPs from Bundibugyo NC_014373, Cote d'Ivoire FJ217162, Sudan NC_006432, Zaire.1995, Zaire.2014 AY354458 and a negative control, VSV glycoprotein (VSVg). The study was done using "MesoScale Discovery" (MSD), a technology that allows binding/fixation of the Ebola strain VLPs (that express the Ebola glycoproteins/viral surface proteins) to a carbon surface followed by an ELISA-type binding assay. The purpose was to identify the binding profiles of the mAbs with respect to various Ebola strains.

[0224] The assay was performed in 96 well polypropylene microwell plates by first preparing a 1:10 dilution of the supernatants from the various VLPs/well (as noted in the following table) and adding the dilutions to PBS (50 µl/well) and incubating at 4° C overnight.

[0225] The liquid in the wells was discarded followed by blocking with 150 µl/well in PBS + 2% BSA and incubating for one hour at room temperature. The contents of each well were then discarded and the wells were washed with PBS using an AquaMax2000 plate washer designated for MSD. Fifty microliters of primary antibody was diluted in PBS +1% BSA and incubated at room temperature with shaking at an intermediate speed (5). The well contents were then discarded and the plates were washed with PBS. Fifty microliters of sulfo-TAG detection reagent (human or mouse Fc) at a concentration of 1 µg/ml in PBS + 0.5% BSA was added to each well and incubated at room temperature for one hour with shaking at an intermediate speed(5). The well contents were discarded and the plates were washed with PBS + 0.5% BSA. To each well was added 150 µl of 1X Read Buffer without surfactant and the

plates were read on a SECTORImager6000 from barcode.

[0226] The results, which are shown in Table 8 below, demonstrate that all of the anti-Ebola virus GP antibodies tested bind to VLPs containing the Zaire 2014 and Zaire 1995 GPs. Certain of the antibodies tested bind to VLPs containing the GPs from other Ebola virus strains, in addition to binding the two Zaire strains noted in Table 8. In particular, in addition to binding to the VLPs containing the GPs from Zaire 2014 and Zaire 1995, the anti-Ebola virus antibodies designated as H1H17161P and H1H17162P bind to VLPs containing the GPs from Sudan and Bundibugyo strains, while the anti-Ebola virus antibodies designated as H2aM17356N and H1H17142P bind to Bundibugyo and Cote d'Ivoire strains.

Table 8: Cross Reactivity of anti-Ebola Virus Antibodies with GPs from Various Strains of Ebola Virus

	Anti-Ebola Virus Antibody Binding to VLPs containing GPs from Various Ebola Virus Strains				
AbPID	**Sudan**	**Bundibugyo**	**Cote d'Ivoire**	**Zaire 2014**	**Zaire 1995**
H1H17161P	+	+	–	+	+
H1H17139P	–	–	–	+	+
H1H17203P	–	–	–	+	+
H1H17219P	–	–	–	+	+
H1H17162P	+	+	–	+	+
H1H17199P	–	–	–	+	+
H1H17193P	–	–	–	+	+
H1M17354N	–	–	–	+	+
H1M17357N	–	–	–	+	+
H1H17134P	–	–	–	+	+
H1H17360N	–	–	–	+	+
H1H17358N2	–	–	–	+	+
H2aM17356N	–	+	+	+	+
H1H17223P	–	–	–	+	+
H1H17196P	–	–	–	+	+
H1H17151P	–	–	–	+	+
H1H17142P	–	+	+	+	+
H1H17214P	–	–	–	+	+
H1H17228P	–	–	–	+	+
H2aM17359N	–	–	–	+	+

Example 9. *In vitro* Neutralization of Live/Infectious Ebola Virus (EBOV)

[0227] Antibodies designated as H1H17203P, H1H17139P and H1H17161P were analyzed for their ability to neutralize infectious EBOV in Vero cells. Vero cells were plated on 384-well plates

in DMEM-10% FBS and allowed to grow to approximately 75% confluence at 37°C. H1H17203P, H1H17139P and H1H17161P were diluted as indicated. EBOV strains (Mayinga, Kikwit, Makona, and guinea pig-adapted Mayinga) were thawed and diluted appropriately to an MOI between 0.01-0.1. A commercially available anti-EBOV antibody designated KZ52 was used as a positive control. (See Maruyama, T. *et al.*, *J Virol* 73, 6024–6030 (1999). Antibodies were incubated with the virus for 1 hour at 37°C. The antibody/virus mix was then added to the pre-plated cells and plates were incubated at 37°C for 24 hours. After the incubation period, plates were removed from the incubator and inactivated by immersing in 10% neutral buffered formalin, placed in a heat sealed bag and stored at 4°C overnight in BSL-4. Plates were washed 3 times in 1X-PBS and cells were permeabilized at room temperature (RT) with 25µl of 0.1% Triton X-100 in 1X-PBS for 15-20 minutes. Triton-X was discarded and the plates were blocked with 3.5% BSA in 1X-PBS for 1 hour at RT. Plates were treated overnight at 4°C with anti-EBOV GP primary antibody 4F3 (See IBT BIOSERVICES for mouse anti-EBOV GP monoclonal antibody 4F3, catalogue number 0201-020) diluted 1:1500 in 1X-PBS. Plates were washed in 1X-PBS for 10-15 minutes and repeated twice. Cells were incubated for 1 hour with Alexa-fluor-488 conjugated anti-mouse secondary antibody. Secondary antibody was discarded and plates were washed in 1X-PBS for 10-15 minutes and repeated twice. Plates were incubated with 25µl/well of Hoechst (1:50,000 in 1X-PBS) for 30 minutes at RT. Plates were imaged by fluorescence microscopy using blue and green fluorescence channels.

Results

[0228] The results, shown in Figure 1, demonstrated that the H1H17161P antibody neutralized live virus and was more potent than the positive control antibody KZ52, but the antibodies designated as H1H17203P and H1H17139P did not act as neutralizers.

Example 10: Binding of anti-Ebola Antibodies to Soluble GP (sGP)

[0229] The fourth gene in the EBOV genome encodes two unique proteins, a non-structural, dimeric secreted glycoprotein, termed sGP, and a trimeric, virion-attached, envelope glycoprotein (GP). These two GPs share the first 295 amino acids, but have unique C termini. To determine if the Regeneron lead mAbs bind to sGP, a recombinant sGP.mmh protein was produced in-house (SEQ ID NO: 317). Interferometry based biosensor Octet HTX was used to determine if H1H17203P, H1H17139P, H1H17161P monoclonal antibodies can bind to the Ebola sGP.mmh protein. The format of the assay involved capturing H1H17203P, H1H17139P, H1H17161P, onto anti-hFc sensor tips, followed by submersion into 300 nM solutions of Ebola GP.10xhis (SEQ ID NO: 318), sGP.mmh (SEQ ID NO: 317), or hCNTFR (ciliary neurotrophic factor receptor.mmh, which is a negative control protein). Each mAb was captured at a level between 0.94 – 1.36 nm.

[0230] As shown in Figure 2, all mAbs showed specific binding to Ebola GP.10xhis and no

binding to the negative control protein; whereas, only H1H17139 demonstrated specific binding to Ebola sGP.mmh. This finding suggests that the binding epitope of H1H17139 is likely located in a common region within the first 295 amino acids of both the sGP and GP; whereas the other mAbs possibly only recognize the C-terminus of Ebola GP.

Example 11: Binding of Additional Anti-EBOV GP Antibodies to Ebola GP.h, Ebola GP soluble.mmh and hCNTFR.mmh

[0231] A further study was done to determine the binding characteristics of additional anti-EBOV GP antibodies of the description; in particular, the study was done to determine the ability of these additional antibodies to bind to soluble GP and GP. This study was done using a real time, label-free bio-layer interferometry (BLI) assay on an Octet HTX biosensor (ForteBio Corp., A Division of Pall Life Sciences). The entire experiment was performed at 25°C in buffer comprised of 0.01M HEPES pH7.4, 0.15M NaCl, 3mM EDTA, 0.05% v/v Surfactant P20, 1.0mg/mL BSA (Octet HBS-ET buffer) with the plate shaking at a speed of 1000rpm. To assess if antibodies were able to bind Ebola sGP or other Ebola GP reagents, approximately ~1.0nm of anti-Ebola GP mAbs were captured onto anti-human Fc (Fortebio Inc, # 18-5064) antibody coated Octet biosensors by submerging the biosensors for 3 minutes into wells containing 20µg/mL solutions of mAbs. The mAb-captured biosensors were tested for binding to selected protein reagents by immersion into wells containing 300nM solutions of Ebola GP proteins or irrelevant controls for 5 minutes. All the biosensors were washed in Octet HBS-ET buffer in between each step of the experiment. The real-time binding response was monitored during the course of the experiment and the binding response at the end of every step was recorded.

Results

[0232] As shown in Table 9, any value below 0.10 nm was determined to be a non-binding antibody. Based on the results to date, all but one of the antibodies (H1H17360N) tested showed binding to EBOV full length GP, and thirteen out of the twenty antibodies tested showed binding to soluble GP (sGP**).**

Table 9: Binding of anti-Ebola GP antibodies to Ebola GP.h., Ebola GP soluble.mmh, and hCNTFR.mmh

Antibody Number	Binding to sGP	300 nM Ebola sGP (F2) Bind (nm)	300 nM Ebola GP.h Bind (nm)	300 nM hCNTFR.mmh (Negative control) Bind (nm)
H1H17161P	No	0.00	0.55	-0.01
H1H17139P	Yes	0.19	0.55	0.01
H1H17203P	No	0.02	0.61	0.01
H1H17219P	No	0.01	0.68	0.01
H1H17162P	No	0.03	0.49	0.02
H1H17199P	Yes	0.33	0.38	0.00
H1H17193P	Yes	0.26	0.33	0.02

H1M17354N	Yes	0.18	0.71	0.02
H1M17357N	No	0.10	0.56	0.01
H1H17134P	No	0.01	0.70	-0.01
H1H17360N	No	0.09	0.09	0.03
H1H17358N2	Yes	0.30	0.35	0.01
H1H17356N	Yes	0.22	0.23	0.02
H1H17223P	Yes	0.31	0.61	0.02
H1H17196P	Yes	0.25	0.62	0.01
H1H17151P	Yes	0.33	0.43	-0.02
H1H17142P	Yes	0.28	0.34	0.01
H1H17214P	Yes	0.38	0.52	0.01
H1H17228P	Yes	0.35	0.58	0.00
H1H17359N	Yes	0.39	0.51	0.00

What is claimed is:

1. An isolated recombinant antibody or antigen-binding fragment thereof that specifically binds to Ebola virus (EBOV) and/or an Ebola virus glycoprotein (EBOV-GP), wherein the antibody or antigen-binding fragment thereof comprises:

(i) an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30; and an LCDR3 amino acid sequence of SEQ ID NO: 32;

(ii) an HCDR1 amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 70; an HCDR3 amino acid sequence of SEQ ID NO: 72; an LCDR1 amino acid sequence of SEQ ID NO: 76; an LCDR2 amino acid sequence of SEQ ID NO: 78; and an LCDR3 amino acid sequence of SEQ ID NO: 80; or

(iii) an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158; and an LCDR3 amino acid sequence of SEQ ID NO: 160.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof has one or more of the following characteristics:

(a) is a fully human monoclonal antibody;

(b) binds to EBOV, or a virus like particle (VLP) expressing an EBOV-GP with a dissociation constant (KD) of less than 10-7M, as measured in a surface plasmon resonance assay;

(c) demonstrates at least a 3 fold increase in dissociative half-life (t½) at pH 5 or pH 6 relative to pH 7.4;

(d) demonstrates neutralization of Zaire Ebola virus with an IC50 ranging from about 10 -11 M to about 10 -9 M;

(e) demonstrates binding to cells expressing the EBOV-GP triggering antibody-dependent cellular cytotoxicity;

(f) cross reacts with one or more strains of EBOV selected from the group consisting of Zaire.2014, Zaire.1995, Sudan, Bundibugyo and Cote d'Ivoire;

(g) binds to soluble GP (sGP);

(h) cross-competes with a reference antibody, wherein the reference antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

3. The isolated antibody or antigen-binding fragment thereof of either claim 1 or 2, comprising an HCVR having an amino acid sequence of SEQ ID NO: 18 and an LCVR having an amino acid sequence of SEQ ID NO: 26.

4. The isolated antibody or antigen-binding fragment thereof of either claim 1 or 2, comprising an HCVR having an amino acid sequence of SEQ ID NO: 66 and an LCVR having an amino acid sequence of SEQ ID NO: 74.

5. The isolated antibody or antigen-binding fragment thereof of either claim 1 or 2, comprising an HCVR having an amino acid sequence of SEQ ID NO: 146 and an LCVR having an amino acid sequence of SEQ ID NO: 154.

6. The isolated antibody or antigen-binding fragment thereof of either claim 1 or claim 2, comprising an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30 and an LCDR3 amino acid sequence of SEQ ID NO: 32.

7. The isolated antibody or antigen-binding fragment thereof of either claim 1 or claim 2, comprising an HCDR1 amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 70; an HCDR3 amino acid sequence of SEQ ID NO: 72; an LCDR1 amino acid sequence of SEQ ID NO: 76; an LCDR2 amino acid sequence of SEQ ID NO: 78 and an LCDR3 amino acid sequence of SEQ ID NO: 80.

8. The isolated antibody or antigen-binding fragment thereof of either claim 1 or claim 2, comprising an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158 and an LCDR3 amino acid sequence of SEQ ID NO: 160.

9. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to the same epitope on EBOV and/or EBOV GP as a reference antibody or antigen-binding fragment comprising:

(i) an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30; and an LCDR3 amino acid sequence of SEQ ID NO: 32;

(ii) an HCDR1 amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 70; an HCDR3 amino acid sequence of SEQ ID NO: 72; an LCDR1 amino acid sequence of SEQ ID NO: 76; an LCDR2 amino acid sequence of SEQ ID NO: 78; and an LCDR3 amino acid sequence of SEQ ID NO: 80; or

(iii) an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158; and an LCDR3 amino acid sequence of SEQ ID NO: 160.

10. The isolated antibody or antigen-binding fragment of any one of claims 1 - 9, wherein the antibody prevents attachment to and/or entry of Ebola virus into a host cell.

11. A method of neutralizing infectious EBOV, the method comprising exposing a cell infected with EBOV to a composition comprising one or more anti-EBOV antibodies or antigen-binding fragments thereof according to any one of claims 1-10, wherein the exposing results in enhanced protection of the cell from virus infection, or from cell death.

12. Use of a composition comprising one or more anti-EBOV antibodies or antigen-binding fragments thereof according to any one of claims 1 - 10 in the manufacture of a medicament for use in a method of neutralizing infectious EBOV, the method comprising exposing a cell infected with EBOV to the composition, wherein the exposing results in enhanced protection of the cell from virus infection, or from cell death.

13. The method of claim 11 or the use of claim 12, wherein the infectious EBOV is neutralized in vitro or in vivo.

14. The method of claim 11 or the use of claim 12, wherein the enhanced protection is observed when the antibody is used alone, or when it is used in combination with one or more additional therapeutic agents or anti-EBOV treatment modalities.

15. The method or use of claim 14, wherein the one or more additional therapeutic agents is selected from the group consisting of an anti-viral drug, an anti-inflammatory drug (e.g. corticosteroids and non-steroidal anti-inflammatory drugs), a different antibody to EBOV, a vaccine for EBOV, TKM Ebola (small interfering RNAs that target viral RNA polymerase), brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537 (antisense phosphorodiamidate morpholino oligomers that target EBOV VP24 gene) and interferons.

16. The method or use of claim 14, wherein the one or more additional therapeutic agents comprise one or more anti-EBOV antibodies.

17. The method or use of claim 16, wherein the one or more anti-EBOV antibodies comprise a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence selected from the group consisting of any of the HCVR and LCVR amino acid sequences of Table 1.

18. The method or use of claim 17, wherein the one or more anti-EBOV antibodies comprise a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298 and 306/282.

19. The method or use of claim 18, wherein the one or more anti-EBOV antibodies comprise a heavy chain variable region (HCVR) and a light chain variable region (LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26, 66/74 and 146/154.

20. A pharmaceutical composition comprising one or more isolated monoclonal antibodies or antigen-binding fragments thereof that bind specifically to EBOV according to any one of claims 1 – 10 and a pharmaceutically acceptable carrier or diluent.

21. The pharmaceutical composition of claim 20, wherein the one or more isolated monoclonal antibodies or antigen-binding fragments thereof comprise an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26, 66/74 and 146/154.

22. A pharmaceutical composition comprising (a) a first anti-EBOV antibody or an antigen-binding fragment thereof according to any one of claims 1 - 10; (b) a second anti-EBOV antibody or antigen-binding fragment thereof; and (c) a third anti-EBOV antibody or antigen-binding fragment thereof, wherein the first antibody binds to, or interacts with, a first epitope on EBOV and the second and/or third antibody binds to, or interact(s) with a different epitope on EBOV, and (d) a pharmaceutically acceptable carrier or diluent.

23. The pharmaceutical composition of claim 22, wherein the first, second and third anti-EBOV antibodies comprise the HCVR/LCVR amino acid sequence pairs of SEQ ID NOs: 18/26, 66/74, and 146/154, respectively.

24. The pharmaceutical composition of claim 22, wherein the epitopes that bind to, or interact with, the first, second and/or third anti-EBOV antibodies or antigen-binding fragments thereof, are distinct and non-overlapping.

25. The pharmaceutical composition of claim 22, wherein the first anti-EBOV antibody or an antigen-binding fragment thereof binds to, or interacts with one epitope on one strain of EBOV and the second and/or third anti-EBOV antibody or an antigen-binding fragment thereof binds to, or interacts with a second and/or a third epitope on the same strain or on a different strain of EBOV.

26. The pharmaceutical composition of claim 25, wherein the EBOV strains are selected from the group consisting of the Zaire.2014, Zaire.1995, Sudan, Bundibugyo, and Cote d'Ivoire strains.

27. A pharmaceutical composition comprising a first isolated monoclonal antibody or an antigen-binding fragment thereof that binds specifically to EBOV, wherein the first isolated monoclonal antibody or an antigen-binding fragment thereof comprises an HCDR1 amino acid sequence of SEQ ID NO: 20; an HCDR2 amino acid sequence of SEQ ID NO: 22; an HCDR3 amino acid sequence of SEQ ID NO: 24; an LCDR1 amino acid sequence of SEQ ID NO: 28; an LCDR2 amino acid sequence of SEQ ID NO: 30 and an LCDR3 amino acid sequence of SEQ ID NO: 32, and a pharmaceutically acceptable carrier or diluent.

28. The pharmaceutical composition of claim 27, further comprising a second isolated monoclonal antibody or an antigen-binding fragment thereof that binds specifically to EBOV, wherein the second isolated monoclonal antibody or an antigen-binding fragment thereof comprises an HCDR1 amino acid sequence of SEQ ID NO: 68; an HCDR2 amino acid sequence of SEQ ID NO: 70; an HCDR3 amino acid sequence of SEQ ID NO: 72; an LCDR1 amino acid sequence of SEQ ID NO: 76; an LCDR2 amino acid sequence of SEQ ID NO: 78 and an LCDR3 amino acid sequence of SEQ ID NO: 80.

29. The pharmaceutical composition of claim 28, further comprising a third isolated monoclonal antibody or an antigen-binding fragment thereof that binds specifically to EBOV, wherein the third isolated monoclonal antibody or an antigen-binding fragment thereof comprises an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158 and an LCDR3 amino acid sequence of SEQ ID NO: 160.

30. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an HCVR, and an LCVR of an antibody as set forth in any one of claims 1 – 10.

31. A vector comprising the polynucleotide sequence of claim 30.

32. A cell expressing the vector of claim 31.

33. A method of preventing, treating or ameliorating at least one symptom of EBOV infection, or of decreasing the frequency or severity of at least one symptom of EBOV infection, the method comprising administering an antibody or antigen-binding fragment thereof of any one of claims 1 – 10 or a pharmaceutical composition of claims 20 - 29 to a subject in need thereof.

34. Use of an antibody or antigen-binding fragment of any one of claims 1 – 10, or a pharmaceutical composition of claims 20 – 29, in the manufacture of a medicament for use in a method of preventing, treating or ameliorating at least one symptom of EBOV infection, or of decreasing the frequency or severity of at least one symptom of EBOV infection, the method comprising administering the antibody or antigen-binding fragment thereof or the pharmaceutical composition to a subject in need thereof.

35. The method of claim 33 or the use of claim 34, the method comprising administering an antibody cocktail comprising a mixture of at least two anti-EBOV antibodies.

36. The method of claim 33 or the use of claim 34, the method comprising administering an antibody cocktail comprising a mixture of three anti-EBOV antibodies, wherein the three anti-EBOV antibodies comprise HCVR/LCVR amino acid sequence pairs as set forth in SEQ ID NOs: 18/26, 66/74 and 146/154.

37. The method of claim 33 or the use of claim 34, wherein the at least one symptom is selected from the group consisting of fever, headache, fatigue, loss of appetite, myalgia, diarrhea, vomiting, abdominal pain, dehydration and unexplained bleeding.

38. The method of claim 33 or the use of claim 34, wherein the antibody or antigen-binding fragment thereof, or the pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, is administered prophylactically or therapeutically to the subject in need thereof.

39. The method of claim 33 or the use of claim 34, wherein the subject in need thereof is a subject suffering from an infection with EBOV, or a subject exposed to, or at risk for exposure to EBOV, or of acquiring an EBOV infection, wherein the subject is selected from the group consisting of an immunocompromised individual, a healthcare worker, a person who is suspected of having been exposed to a person harboring the Ebola virus, a person who comes into physical contact or close physical proximity with an infected individual, a hospital employee, a pharmaceutical researcher, maintenance personnel responsible for cleaning a hospital facility or institution where an Ebola patient has been treated, individuals who have visited or are planning to visit an area or country known to have or suspected to have an outbreak of Ebola virus and a frequent flyer.

40. The method or use of any one of claims 33 - 39, wherein the antibody or antigen-binding fragment thereof, or the pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, is administered in combination with a second therapeutic agent.

41. The method or use of claim 40, wherein the second therapeutic agent is selected from the group consisting of an anti-viral drug, an anti-inflammatory drug (e.g. corticosteroids and non-steroidal anti-inflammatory drugs), a different antibody to EBOV, a vaccine for EBOV, TKM Ebola (small interfering RNAs that target viral RNA polymerase), brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537, (antisense phosphorodiamidate morpholino oligomers that target Ebola virus VP24 gene) and interferons.

42. The method of claim 33 or the use of claim 34, wherein the pharmaceutical composition is administered subcutaneously, intravenously, intradermally, intramuscularly, intranasally, or orally.

43. A method of increasing survival, or the likelihood of survival, of a subject suffering from infection with EBOV, or a subject exposed to EBOV, or at risk for exposure to, or for acquiring EBOV, the method comprising administering at least one antibody or antigen-binding fragment thereof of any one of claims 1 – 10, or a pharmaceutical composition of any of claims 20 - 29 to a subject in need thereof.

44. Use of an antibody or antigen-binding fragment thereof of any one of claims 1 – 10, or a pharmaceutical composition of any of claims 20 - 29, in the manufacture of a medicament for use in a method of increasing survival, or the likelihood of survival of a subject suffering from infection with EBOV, or a subject exposed to EBOV, or at risk for exposure to, or for acquiring EBOV, the method comprising administering at least one antibody or antigen-binding fragment, or the pharmaceutical composition to a subject in need thereof.

45. The method of claim 43 or the use of claim 44, wherein the method comprises administering an antibody cocktail comprising a mixture of at least two anti-EBOV antibodies.

46. The method of claim 43 or the use of claim 44, the method comprising administering an antibody cocktail comprising a mixture of three anti-EBOV antibodies, wherein the three anti-EBOV antibodies comprise HCVR/LCVR amino acid sequence pairs as set forth in SEQ ID NOs: 18/26, 66/74 and 146/154.

47. The method or use of any one of claims 43 - 46, wherein the antibody or antigen-binding fragment thereof, or the pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, or the antibody cocktail, is administered prophylactically or therapeutically to the subject in need thereof.

48. The method or use of any one of claims 43 - 47, wherein the subject in need thereof who is at risk for exposure to, or for acquiring an EBOV infection is selected from the group consisting of an immunocompromised individual, a healthcare worker, a person who is suspected of having been exposed to a person harboring the Ebola virus, a person who comes into physical contact or close physical proximity with an infected individual, a hospital employee, a pharmaceutical researcher, maintenance personnel responsible for cleaning a hospital facility or institution where an Ebola patient has been treated, individuals who have visited or are planning to visit an area or country known to have or suspected to have an outbreak of Ebola virus and a frequent flyer.

49. The method or use of any one of claims 43 – 48, wherein the antibody or antigen-binding fragment thereof, or the pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, or the antibody cocktail, is administered in combination with a second therapeutic agent.

50. The method or use of claim 49, wherein the second therapeutic agent is selected from the group consisting of an anti-viral drug, an anti-inflammatory drug (e.g. corticosteroids and non-steroidal anti-inflammatory drugs), a different antibody to EBOV, a vaccine for EBOV, TKM Ebola (small interfering RNAs that target viral RNA polymerase), brincidofovir (CMX-001), favipiravir (T-705), BCX-4430, AVI-7537, (antisense phosphorodiamidate morpholino oligomers that target Ebola virus VP24 gene), and interferons.

51. The method or use of any one of claims 44 - 50, wherein the pharmaceutical composition is administered subcutaneously, intravenously, intradermally, intramuscularly, intranasally, or orally.

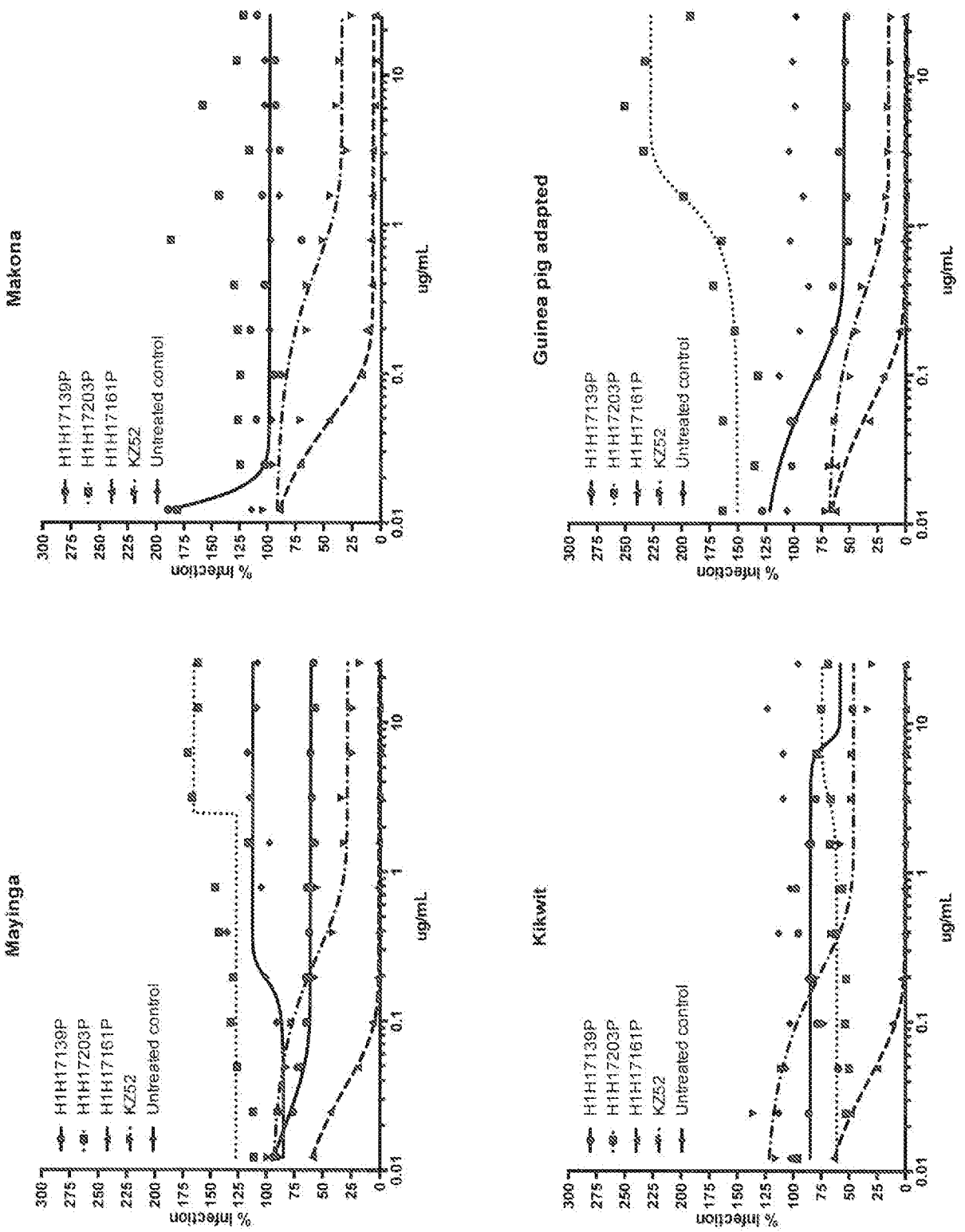
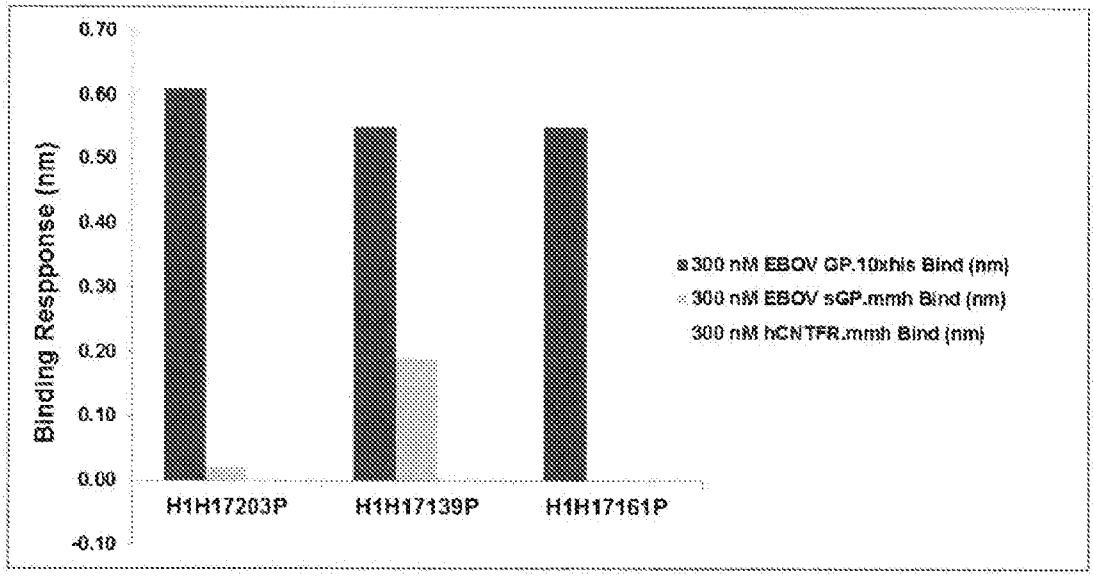

Makona
Mayinga
Guinea pig adapted
Kikwit
H1H17139P
H1H17203P
H1H17161P
KZ52
Untreated control
% infection
ug/mL

Figure 1

Figure 2: Interaction of H1H17203, H1H17139P and H1H17161P with Ebola GP.10xhis and Ebola soluble GP (sGP.mmh) at 25 °C



Octet HTX binding signals for each of the Ebola GP antibodies to 300nM Ebola GP.10xhis (black), Ebola soluble sGP.mmh (dark grey), and the irrelevant, negative control protein hCNTFR.mmh (light gray).

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

<210> 43
<211> 18
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<220>
<223> synthetic

<400> 43

cagggcatta gaattgat 18

<210> 44
<211> 6
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<220>
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<400> 44
Gln Gly Ile Arg Ile Asp
1 5

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

<220>
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<400> 45
gctgcatcc 9

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

<220>
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<400> 46
Ala Ala Ser
1

<210> 47
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
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<400> 47
ctacagcaaa atagttaccc gtggacg 27

<210> 48
<211> 9
<212> PRT
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<220>
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<400> 48

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Leu Gln Gln Asn Ser Tyr Pro Trp Thr
 1               5


<210> 49
<211> 387
<212> DNA
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<220>
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<400> 49
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tcctgtgcag cctctggatt cacctttagc agctatgcca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt attagtggta gtggtggttg gagaaactac 180
gcagactccg tgaagggccg gatcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acaacctgag agccgaggac acggccgtat attattgtgc gaaagatcgg 300
ggtgcgactt ttggagtggt tattttggga ccccccctatt acggtatgga cgtctggggc 360
caagggacca cggtcaccgt ctcctca                                     387

<210> 50
<211> 129
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<220>
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<400> 50
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
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Val Ile Ser Gly Ser Gly Gly Trp Arg Asn Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Ile Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Asp Arg Gly Ala Thr Phe Gly Val Val Ile Leu Gly Pro Pro
            100                 105                 110
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
        115                 120                 125
Ser



<210> 51
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<400> 51
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ggattcacct ttagcagcta tgcc 24

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

<220>
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<400> 52
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

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

<220>
<223> synthetic

<400> 53
attagtggta gtggtggttg gaga 24

<210> 54
<211> 8
<212> PRT
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<220>
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<400> 54
Ile Ser Gly Ser Gly Gly Trp Arg
1 5

<210> 55
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
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<400> 55
gcgaaagatc ggggtgcgac ttttggagtg gttattttgg gacccccta ttacggtatg 60
gacgtc 66

<210> 56
<211> 22
<212> PRT
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<220>
<223> synthetic

<400> 56
Ala Lys Asp Arg Gly Ala Thr Phe Gly Val Val Ile Leu Gly Pro Pro
 1   5   10   15
Tyr Tyr Gly Met Asp Val
            20

<210> 57
<211> 321
<212> DNA
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<220>
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<400> 57
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atcacttgcc gggcaagtca gagcattagc acttatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacaggt ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa 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 Ser Leu Ser Ala Ser Val Arg
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ile Pro Tyr
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 59
<211> 18
<212> DNA
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<220>
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<400> 59
cagagcatta gcacttat   18

<210> 60
<211> 6
<212> PRT
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<220>
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<400> 60
Gln Ser Ile Ser Thr Tyr
 1   5

<210> 61
<211> 9
<212> DNA
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<220>
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<400> 61
gctgcatcc   9

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

<220>
<223> synthetic

<400> 62
Ala Ala Ser
 1

<210> 63
<211> 27
<212> DNA
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<220>
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<400> 63
caacagagtt acagtatccc gtacact   27

<210> 64
<211> 9
<212> PRT
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<220>
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<400> 64
Gln Gln Ser Tyr Ser Ile Pro Tyr Thr
 1   5

<210> 65
<211> 354
<212> DNA
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<220>
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<400> 65
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tcctgtgcag cctctggatt cacctctagc agctatgcca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaaca attagtggta tgggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaagggga 300
tatccccatt cttttgatat ctggggccaa gggacaatgg tcaccgtctc ttca 354

<210> 66
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

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

<210> 67
<211> 24
<212> DNA
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<220>
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<400> 67
ggattcacct ctagcagcta tgcc 24

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

<220>
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<400> 68
Gly Phe Thr Ser Ser Ser Tyr Ala
 1   5

<210> 69
<211> 24
<212> DNA
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<220>
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<400> 69
attagtggta tgggtggtag caca   24

<210> 70
<211> 8
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<220>
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<400> 70
Ile Ser Gly Met Gly Gly Ser Thr
 1   5

<210> 71
<211> 33
<212> DNA
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<220>
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<400> 71
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<210> 72
<211> 11
<212> PRT
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<220>
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<400> 72
Ala Lys Arg Gly Tyr Pro His Ser Phe Asp Ile
 1   5   10

<210> 73

<211> 318
<212> DNA
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<220>
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atcacttgcc gggcaagtca gagcattagc agcttttaa attggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta ccctcacctt cggccaaggg 300
acacgactgg agattaaa 318

<210> 74
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

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

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

<220>
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<400> 75
cagagcatta gcagcttt 18

<210> 76
<211> 6
<212> PRT
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<220>
<223> synthetic

<400> 76
Gln Ser Ile Ser Ser Phe
 1   5

<210> 77
<211> 9
<212> DNA
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<220>
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<400> 77
gctgcatcc   9

<210> 78
<211> 3
<212> PRT
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<400> 78
Ala Ala Ser
 1

<210> 79
<211> 24
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<220>
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<400> 79
caacagagtt acagtaccct cacc   24

<210> 80
<211> 8
<212> PRT
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<220>
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<400> 80
Gln Gln Ser Tyr Ser Thr Leu Thr
 1   5

<210> 81
<211> 354
<212> DNA
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<220>

<223> synthetic

<400> 81
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ccagggaagg ggctggagtg ggtctcagct attagtggta gtagtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaaaaa gacgctgtat 240
ctacaaatga acagcctgag agtcgaggac acggccgtat attactgtgc gaaaggggg 300
taccccatt cttttgatat ctggggccat gggacaatgg tcaccgtctc ttca 354

<210> 82
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
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<400> 82
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 Glu Phe Thr Phe Ser Ser Tyr
            20   25   30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ala Ile Ser Gly Ser Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Gly Gly Tyr Pro His Ser Phe Asp Ile Trp Gly His Gly Thr
            100   105   110
Met Val Thr Val Ser Ser
        115

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

<220>
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<400> 83
gaattcacct ttagcagcta tgcc 24

<210> 84
<211> 8
<212> PRT
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<220>
<223> synthetic

<400> 84
Glu Phe Thr Phe Ser Ser Tyr Ala
 1   5

<210> 85
<211> 24
<212> DNA
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<220>
<223> synthetic

<400> 85
attagtggta gtagtggtag caca 24

<210> 86
<211> 8
<212> PRT
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<220>
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<400> 86
Ile Ser Gly Ser Ser Gly Ser Thr
1 5

<210> 87
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<212> DNA
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<220>
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<400> 87
gcgaaagggg ggtaccccca ttcttttgat atc 33

<210> 88
<211> 11
<212> PRT
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<220>
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<400> 88
Ala Lys Gly Gly Tyr Pro His Ser Phe Asp Ile
1 5 10

<210> 89
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<212> DNA
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<220>
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<400> 89

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atcacttgcc gggcaagtca gagcattagc agcttttaa attggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagtt ccatcacctt cggccaaggg 300
acacgactgg agattaaa                                               318

<210> 90
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
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<400> 90
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Phe
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Ile Thr
                85                  90                  95
Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105


<210> 91
<211> 18
<212> DNA
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<220>
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<400> 91
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<210> 92
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<400> 92
Gln Ser Ile Ser Ser Phe
 1               5


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

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<400> 93
gctgcatcc 9

<210> 94
<211> 3
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<220>
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<400> 94
Ala Ala Ser
 1

<210> 95
<211> 24
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<220>
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<400> 95
caacagagtt acagttccat cacc 24

<210> 96
<211> 8
<212> PRT
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<220>
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<400> 96
Gln Gln Ser Tyr Ser Ser Ile Thr
 1   5

<210> 97
<211> 375
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 97
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tcctgtgcag cgtctggatt caccttcagt agttatggca tccactgggt ccgccaggct 120
ccaggcaagt ggctggagtg ggtggcattt atatggtttg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagacg attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagagatgga 300

gagatttttg gagtgcttat ttcctctgat gcttttgata tctggggcca agggacaatg 360
gtcaccgtct cttca 375

<210> 98
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
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<400> 98
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Trp Leu Glu Trp Val
        35   40   45
Ala Phe Ile Trp Phe Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Asp Gly Glu Ile Phe Gly Val Leu Ile Ser Ser Asp Ala Phe
            100   105   110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120   125

<210> 99
<211> 24
<212> DNA
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<220>
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<400> 99
ggattcacct tcagtagtta tggc 24

<210> 100
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<400> 100
Gly Phe Thr Phe Ser Ser Tyr Gly
 1   5

<210> 101
<211> 24
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<400> 101
atatggtttg atggaagtaa taaa 24

<210> 102
<211> 8
<212> PRT
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<220>
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<400> 102
Ile Trp Phe Asp Gly Ser Asn Lys
 1 5

<210> 103
<211> 54
<212> DNA
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<220>
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<210> 104
<211> 18
<212> PRT
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<220>
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<400> 104
Ala Arg Asp Gly Glu Ile Phe Gly Val Leu Ile Ser Ser Asp Ala Phe
 1 5 10 15
Asp Ile

<210> 105
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
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<400> 105
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atcacttgcc gggcaagtcg gggcattaga aatgatttag gctggtttca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgtt gcatccaatt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt acccgatcac cttcggccaa 300

gggacacgac tggagattaa a 321

<210> 106
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<400> 106
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 Arg Gly Ile Arg Asn Asp
            20   25   30
Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
        35   40   45
Tyr Val Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Ile
                85   90   95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 107
<211> 18
<212> DNA
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<220>
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<400> 107
cggggcatta gaaatgat 18

<210> 108
<211> 6
<212> PRT
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<220>
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<400> 108
Arg Gly Ile Arg Asn Asp
 1   5

<210> 109
<211> 9
<212> DNA
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<220>
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<400> 109
gttgcatcc 9

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

<220>
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<400> 110
Val Ala Ser
 1

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

<220>
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<400> 111
ctacagcata atagttaccc gatcacc 27

<210> 112
<211> 9
<212> PRT
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<220>
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<400> 112
Leu Gln His Asn Ser Tyr Pro Ile Thr
 1   5

<210> 113
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
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<400> 113
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tcctgtgcag cctctggatt caccttcaga agctacgaca tgcactgggt ccgccaaggt 120
tcaggaaaag gtctggagtg ggtctcagct attggtactg ctggtgacac atactattta 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agcgtggttc 300
ggggacgtat tcctggacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 114
<211> 118
<212> PRT

<213> Artificial Sequence

<220>
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<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 Arg Ser Tyr
            20   25   30
Asp Met His Trp Val Arg Gln Gly Ser Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ala Ile Gly Thr Ala Gly Asp Thr Tyr Tyr Leu 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 Ala Trp Phe Gly Asp Val Phe Leu Asp Tyr Trp Gly Gln Gly Thr
            100   105   110
Leu Val Thr Val Ser Ser
        115

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

<220>
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<400> 115
ggattcacct tcagaagcta cgac   24

<210> 116
<211> 8
<212> PRT
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<220>
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<400> 116
Gly Phe Thr Phe Arg Ser Tyr Asp
 1   5

<210> 117
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
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<400> 117
attggtactg ctggtgacac a   21

<210> 118
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 118
Ile Gly Thr Ala Gly Asp Thr
 1   5

<210> 119
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 119
gcaagagcgt ggttcgggga cgtattcctg gactac   36

<210> 120
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 120
Ala Arg Ala Trp Phe Gly Asp Val Phe Leu Asp Tyr
 1   5   10

<210> 121
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 121
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catatatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg caggctatta ctgtcagcag tataataaca ggctgacttt cggcggaggg 300
accaaggtgg agatcaaa   318

<210> 122
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic

<400> 122
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80
Glu Asp Phe Ala Gly Tyr Tyr Cys Gln Gln Tyr Asn Asn Arg Leu Thr
                85   90   95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

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

<220>
<223> synthetic

<400> 123
cagagtgtta gcagcaac 18

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

<220>
<223> synthetic

<400> 124
Gln Ser Val Ser Ser Asn
 1   5

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

<220>
<223> synthetic

<400> 125
ggtgcatcc 9

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

<220>
<223> synthetic

<400> 126
Gly Ala Ser
 1

<210> 127
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 127
cagcagtata ataacaggct gact 24

<210> 128
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

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

<210> 129
<211> 381
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 129
gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gaccactaca tggtctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggttggccgt actagaaaca aagctaatag ttatagcaca 180
gaatatgccg cgtctgtgaa aggcagattc accatctcaa gagatgattc aaagaagtca 240
ctgtatctgc aaatgaacag cctgaaaacc gaggacacgg ccgtgtatta ctgtgctaga 300
ggggggggaaa cactatggtt cggggagtcc aactacggta tggacgtctg gggccaaggg 360
accacggtca ccgtctcctc a 381

<210> 130
<211> 127
<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 Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp His
            20                  25                  30
Tyr Met Val Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Gly Arg Thr Arg Asn Lys Ala Asn Ser Tyr Ser Thr Glu Tyr Ala Ala
    50                  55                  60
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Lys Ser
65                  70                  75                  80
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95
Tyr Cys Ala Arg Gly Gly Glu Thr Leu Trp Phe Gly Glu Ser Asn Tyr
            100                 105                 110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

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

<220>
<223> synthetic

<400> 131
ggattcacct tcagtgacca ctac 24

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

<220>
<223> synthetic

<400> 132
```
Gly Phe Thr Phe Ser Asp His Tyr
 1               5
```

<210> 133
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 133
actagaaaca aagctaatag ttatagcaca 30

<210> 134
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 134
Thr Arg Asn Lys Ala Asn Ser Tyr Ser Thr
 1   5   10

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

<220>
<223> synthetic

<400> 135
gctagagggg gggaaacact atggttcggg gagtccaact acggtatgga cgtc   54

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

<220>
<223> synthetic

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

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

<220>
<223> synthetic

<400> 137
gaaattgtgt tgacgcagtc tccagacacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcacctact tagcctggta ccagcagaaa 120
cctggccagg ctcccagtct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagcgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta ggtcacctct cactttcggc 300
ggagggacca aggtggagat caaa   324

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

<220>
<223> synthetic

<400> 138
Glu Ile Val Leu Thr Gln Ser Pro Asp 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 Thr
            20                  25                  30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ser 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 Arg Ser Pro
                85                  90                  95
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 139
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 139
cagagtgtta gcagcaccta c 21

<210> 140
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 140
```
Gln Ser Val Ser Ser Thr Tyr
 1               5
```

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

<220>
<223> synthetic

<400> 141
ggtgcatcc 9

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

<220>
<223> synthetic

<400> 142
```
Gly Ala Ser
```

1

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

<220>
<223> synthetic

<400> 143
cagcagtatg gtaggtcacc tctcact 27

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

<220>
<223> synthetic

<400> 144
Gln Gln Tyr Gly Arg Ser Pro Leu Thr
1 5

<210> 145
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 145
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggctt caccttcaat aactatggca tgcactgggt ccgccaggct 120
ccaggcatgg ggctggagtg ggtggcagtt atatggcacg atggaagtga taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaaattgg 300
aacctctttg actactgggg ccagggaacc ctggtcactg tctcctca 348

<210> 146
<211> 116
<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 Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Met Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp His Asp Gly Ser Asp Lys Tyr Tyr Ala Asp Ser Val

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

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

<220>
<223> synthetic

<400> 147
ggcttcacct tcaataacta tggc 24

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

<220>
<223> synthetic

<400> 148
```
Gly Phe Thr Phe Asn Asn Tyr Gly
 1               5
```

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

<220>
<223> synthetic

<400> 149
atatggcacg atggaagtga taaa 24

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

<220>
<223> synthetic

<400> 150
```
Ile Trp His Asp Gly Ser Asp Lys
 1               5
```

<210> 151
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 151
gcgagaaatt ggaacctctt tgactac 27

<210> 152
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 152
Ala Arg Asn Trp Asn Leu Phe Asp Tyr
1 5

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

<220>
<223> synthetic

<400> 153
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagaatcacc 60
atcacttgcc gggcaagtca gagcatcagc acctatttac attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccactt tgcagagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agtttcagta cccctccgat aaacttcggc 300
caagggacca agctggagat caaa 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 Ile Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Tyr
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala 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 Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Thr Pro Pro
85 90 95
Ile Asn Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

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

<220>
<223> synthetic

<400> 155
cagagcatca gcacctat 18

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

<220>
<223> synthetic

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

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

<220>
<223> synthetic

<400> 157
gctgcatcc 9

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

<220>
<223> synthetic

<400> 158
Ala Ala Ser
1

<210> 159
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 159
caacagagtt tcagtacccc tccgataaac 30

<210> 160
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 160
Gln Gln Ser Phe Ser Thr Pro Pro Ile Asn
1 5 10

<210> 161
<211> 384
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 161
gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggGTC cctgagactc 60
tcctgtgcag cctctaaatt cacctttgac acctttgcca tgagctgggt ccgccaggct 120
ccagggaagg ggttggaatg ggtctcattt attagtagtt ctggtggtcg cacagactat 180
gtagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa caccctgtat 240
ctgcaaatga acagcctgcg agccgaggac acggccgtat attactgtgc gaaagaacgg 300
acgatttttg gagtgcttat tctgggcccc gacaactacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

<210> 162
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

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

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

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

<220>
<223> synthetic

<400> 163
aaattcacct ttgacacctt tgcc 24

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

<220>
<223> synthetic

<400> 164
Lys Phe Thr Phe Asp Thr Phe Ala
1 5

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

<220>
<223> synthetic

<400> 165
attagtagtt ctggtggtcg caca 24

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

<220>
<223> synthetic

<400> 166
Ile Ser Ser Ser Gly Gly Arg Thr
1 5

<210> 167
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 167
gcgaaagaac ggacgatttt tggagtgctt attctgggcc ccgacaacta cggtatggac 60
gtc 63

<210> 168
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 168
Ala Lys Glu Arg Thr Ile Phe Gly Val Leu Ile Leu Gly Pro Asp Asn
 1   5   10   15
Tyr Gly Met Asp Val
            20

<210> 169
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 169
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ttgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc acctatttaa attggtatca gcaaaaacca 120
gggaaagccc ctaaactcct gatctatgct gcatccagtt tgcaaagtgg ggtctcatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagtg ccctccgat caccttcggc 300
caagggacac gactggagat taaa 324

<210> 170
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 170
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 Ser Ile Ser Thr Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Ser Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ala Pro Pro
                85   90   95
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

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

<220>
<223> synthetic

<400> 171
cagagcatta gcacctat 18

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

<220>
<223> synthetic

<400> 172
Gln Ser Ile Ser Thr Tyr
 1   5

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

<220>
<223> synthetic

<400> 173
gctgcatcc 9

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

<220>
<223> synthetic

<400> 174
Ala Ala Ser
 1

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

<220>
<223> synthetic

<400> 175

caacagagtt acagtgcccc tccgatcacc 30

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

<220>
<223> synthetic

<400> 176
Gln Gln Ser Tyr Ser Ala Pro Pro Ile Thr
1 5 10

<210> 177
<211> 384
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 177
caggtacagc tgcagcagtc aggtccagga ctggtgaagc cctcgcagac cctctcactc 60
acctgtgcca tctccgggga cagtgtctct agcaacattc ctgcttggaa ctggatcagg 120
cagtcccctt cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180
aatgattatg cagtatctgt gaaaagtcga ataaccatca atccagacac atccaagaac 240
cacttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
agaggaaggg tctatgacag gtcttctagg tacttctacg ctatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

<210> 178
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 178
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
Ile Pro Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80
His Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95
Tyr Tyr Cys Ala Arg Gly Arg Val Tyr Asp Arg Ser Ser Arg Tyr Phe
100 105 110
Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 179
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 179
ggggacagtg tctctagcaa cattcctgct 30

<210> 180
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 180
Gly Asp Ser Val Ser Ser Asn Ile Pro Ala
1 5 10

<210> 181
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 181
acatactaca ggtccaagtg gtataat 27

<210> 182
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 182
Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn
1 5

<210> 183
<211> 54
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 183
gcaagaggaa gggtctatga caggtcttct aggtacttct acgctatgga cgtc 54

<210> 184
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 184
Ala Arg Gly Arg Val Tyr Asp Arg Ser Ser Arg Tyr Phe Tyr Ala Met
 1   5   10   15
Asp Val

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

<220>
<223> synthetic

<400> 185
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta attatccgat caccttcggc 300
caagggacac gactggagat taaa   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 Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Asn Tyr Pro
                85   90   95
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 187
<211> 18
<212> DNA

<213> Artificial Sequence

<220>
<223> synthetic

<400> 187
cagagcatta gcagctat 18

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

<220>
<223> synthetic

<400> 188
Gln Ser Ile Ser Ser Tyr
 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> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 191
caacagagtt acagtaatta tccgatcacc 30

<210> 192
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic

<400> 192
Gln Gln Ser Tyr Ser Asn Tyr Pro Ile Thr
 1   5   10

<210> 193
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 193
gaggtgcagc tggtggagtc tgggggaggc ttggttcagc cgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcaga acctacgaca tgcactgggt ccgccaagct 120
acaggaaaag gtctggagtg ggtctcagct attggtactg ctggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gcctgagagc cggtgacacg gctgtgtatt actgtgcacg aacgattttt 300
ggagtggttc ttacctttga ctactggggc cagggaaccc tggtcaccgt ctcctca   357

<210> 194
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 194
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 Arg Thr 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 Ala Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
    50   55   60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
65   70   75   80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95
Arg Thr Ile Phe Gly Val Val Leu Thr Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

<220>

<223> synthetic

<400> 195
ggattcacct tcagaaccta cgac 24

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

<220>
<223> synthetic

<400> 196
Gly Phe Thr Phe Arg Thr Tyr Asp
1 5

<210> 197
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 197
attggtactg ctggtgacac a 21

<210> 198
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 198
Ile Gly Thr Ala Gly Asp Thr
1 5

<210> 199
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 199
gcacgaacga tttttggagt ggttcttacc tttgactac 39

<210> 200
<211> 13
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic

<400> 200
Ala Arg Thr Ile Phe Gly Val Val Leu Thr Phe Asp Tyr
 1   5   10

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

<220>
<223> synthetic

<400> 201
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc agctctttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcacagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag acttacagta tccctccgac caccttcggc 300
caagggacca aggtggaaat caaa   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 Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ser Ile Pro Pro
                85   90   95
Thr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

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

<220>
<223> synthetic

<400> 203
cagagcatta gcagctct   18

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

<220>
<223> synthetic

<400> 204
Gln Ser Ile Ser Ser Ser
 1   5

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

<220>
<223> synthetic

<400> 205
gctgcatcc   9

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

<220>
<223> synthetic

<400> 206
Ala Ala Ser
 1

<210> 207
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 207
caacagactt acagtatccc tccgaccacc   30

<210> 208
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 208
Gln Gln Thr Tyr Ser Ile Pro Pro Thr Thr
 1   5   10

<210> 209
<211> 384
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 209
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc aactatgcca tgatctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaggt attagtggta gtggtggcag tatatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagaagga 300
attattagta tggttcgggg acttatcaac tactaccacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

<210> 210
<211> 128
<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 Asn Tyr
            20   25   30
Ala Met Ile Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gly Ile Ser Gly Ser Gly Gly 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 Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Glu Gly Ile Ile Ser Met Val Arg Gly Leu Ile Asn Tyr Tyr
            100   105   110
His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120   125

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

<220>
<223> synthetic

<400> 211
ggattcacct ttagcaacta tgcc 24

<210> 212
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

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

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

<220>
<223> synthetic

<400> 213
attagtggta gtggtggcag tata   24

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

<220>
<223> synthetic

<400> 214
Ile Ser Gly Ser Gly Gly Ser Ile
 1   5

<210> 215
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 215
gcgaaagaag gaattattag tatggttcgg ggacttatca actactacca cggtatggac 60
gtc   63

<210> 216
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 216
Ala Lys Glu Gly Ile Ile Ser Met Val Arg Gly Leu Ile Asn Tyr Tyr
 1   5   10   15
His Gly Met Asp Val

20

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

<220>
<223> synthetic

<400> 217
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcaccttg gacgttcggc 300
caagggacca aggtggaaat caaa 324

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

<220>
<223> synthetic

<400> 218
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 Pro
                85   90   95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 219
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 219
cagagtgtta gcagcagcta c 21

<210> 220
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 220
Gln Ser Val Ser Ser Ser Tyr
 1   5

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

<220>
<223> synthetic

<400> 221
ggtgcatcc   9

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

<220>
<223> synthetic

<400> 222
Gly Ala Ser
 1

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

<220>
<223> synthetic

<400> 223
cagcagtatg gtagctcacc ttggacg   27

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

<220>
<223> synthetic

<400> 224
Gln Gln Tyr Gly Ser Ser Pro Trp Thr
 1   5

<210> 225
<211> 360

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 225
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60
tcctgcaagg catctggata caccttcacc agctactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gttgggaata atcaacccta gtggtggtag cacaagctac 180
gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagagaca 300
ggagaagctg gtgaggtttt taactactgg ggccagggaa cccaggtcac cgtctcctca 360

<210> 226
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 226
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu
        35   40   45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Thr Gly Glu Ala Gly Glu Val Phe Asn Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser
        115   120

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

<220>
<223> synthetic

<400> 227
ggatacacct tcaccagcta ctat   24

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

<220>

<223> synthetic

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

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

<220>
<223> synthetic

<400> 229
atcaacccta gtggtggtag caca   24

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

<220>
<223> synthetic

<400> 230
Ile Asn Pro Ser Gly Gly Ser Thr
 1   5

<210> 231
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 231
gcgagagaga caggagaagc tggtgaggtt tttaactac   39

<210> 232
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 232
Ala Arg Glu Thr Gly Glu Ala Gly Glu Val Phe Asn Tyr
 1   5   10

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

<220>
<223> synthetic

<400> 233
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gatcattagc aggtatttaa attggtatca gcataaacca 120
gggaaagccc ctaaggtcct gatctatgct gcctccactt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta ccccctccgat caccttcggc 300
caagggacac gactggagat taaa 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 Gln Ile Ile Ser Arg Tyr
            20   25   30
Leu Asn Trp Tyr Gln His Lys Pro Gly Lys Ala Pro Lys Val 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 Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85   90   95
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

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

<220>
<223> synthetic

<400> 235
cagatcatta gcaggtat 18

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

<220>
<223> synthetic

<400> 236
Gln Ile Ile Ser Arg Tyr
 1   5

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

<220>
<223> synthetic

<400> 237
gctgcctcc 9

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

<220>
<223> synthetic

<400> 238
Ala Ala Ser
 1

<210> 239
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 239
caacagagtt acagtacccc tccgatcacc 30

<210> 240
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 240
Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
 1   5   10

<210> 241
<211> 381
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 241

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agttatgaaa tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attggtagta gtggtcgtgc cacatactac 180
gcagactctg tgaagggccg attcaccatc tccagagaca acgccaaaaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagaccttcg 300
agcatagcag ctctgttacg gaaccagtac cacttcggta tggacgtctg gggccaaggg 360
accacggtca ccgtctcctc a 381

<210> 242
<211> 127
<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 Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Tyr Ile Gly Ser Ser Gly Arg Ala Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Pro Ser Ser Ile Ala Ala Leu Leu Arg Asn Gln Tyr His Phe
            100   105   110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120   125

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

<220>
<223> synthetic

<400> 243
ggattcacct tcagtagtta tgaa 24

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

<220>
<223> synthetic

<400> 244
Gly Phe Thr Phe Ser Ser Tyr Glu
 1   5

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

<220>
<223> synthetic

<400> 245
attggtagta gtggtcgtgc caca 24

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

<220>
<223> synthetic

<400> 246
Ile Gly Ser Ser Gly Arg Ala Thr
 1 5

<210> 247
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 247
gcgagacctt cgagcatagc agctctgtta cggaaccagt accacttcgg tatggacgtc 60

<210> 248
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 248
Ala Arg Pro Ser Ser Ile Ala Ala Leu Leu Arg Asn Gln Tyr His Phe
 1 5 10 15
Gly Met Asp Val
 20

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

<220>
<223> synthetic

<400> 249
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattacc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaggtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta ccctccgat caccttcggc 300
caagggacac gactggagat taaa 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 Gln Ser Ile Thr Ser Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85   90   95
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

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

<220>
<223> synthetic

<400> 251
cagagcatta ccagctat 18

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

<220>
<223> synthetic

<400> 252
Gln Ser Ile Thr Ser Tyr
 1   5

<210> 253
<211> 9

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 253
gctgcatcc 9

<210> 254
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 254
Ala Ala Ser
1

<210> 255
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 255
caacagagtt acagtacccc tccgatcacc 30

<210> 256
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 256
Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
1 5 10

<210> 257
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 257
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60
tcctgcaagg catctggata caccttcacc agctactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaata atcaacccta gtggtggtag cacaagctac 180
gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagagata 300
ggagaagctg gtgaagtttt taactactgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 258
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 258
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Ile Gly Glu Ala Gly Glu Val Phe Asn Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 259
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 259
ggatacacct tcaccagcta ctat   24

<210> 260
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 260
Gly Tyr Thr Phe Thr Ser Tyr Tyr
 1   5

<210> 261
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 261
atcaacccta gtggtggtag caca 24

<210> 262
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 262
Ile Asn Pro Ser Gly Gly Ser Thr
1 5

<210> 263
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 263
gcgagagaga taggagaagc tggtgaagtt tttaactac 39

<210> 264
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 264
Ala Arg Glu Ile Gly Glu Ala Gly Glu Val Phe Asn Tyr
1 5 10

<210> 265
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 265
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc aggtatttaa attggtatca gcataaacca 120
gggaaagccc ctaaggtcct gatctatgct gcatccattt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300
caagggacac gactggagat taaa 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 Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Tyr
            20   25   30
Leu Asn Trp Tyr Gln His Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
        35   40   45
Tyr Ala Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85   90   95
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 267
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 267
cagagcatta gcaggtat   18

<210> 268
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 268
Gln Ser Ile Ser Arg Tyr
 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> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 271
caacagagtt acagtacccc tccgatcacc 30

<210> 272
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 272
Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
 1   5   10

<210> 273
<211> 381
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 273
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt acttatgaaa tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatat agtagtagta gtggtagaac catatactac 180
gcagactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgttt 240
ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagaccttcg 300
agtatagaga ctctgttacg gaatcagtac cactacggtg tggacgtctg gggccaaggg 360
accacggtca ccgtctcctc a 381

<210> 274
<211> 127
<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 Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20   25   30
Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Tyr Ser Ser Ser Ser Gly Arg Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Pro Ser Ser Ile Glu Thr Leu Leu Arg Asn Gln Tyr His Tyr
            100   105   110
Gly Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120   125

<210> 275
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 275
ggattcacct tcagtactta tgaa   24

<210> 276
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 276
Gly Phe Thr Phe Ser Thr Tyr Glu
 1   5

<210> 277
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 277
agtagtagta gtggtagaac cata   24

<210> 278
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 278
Ser Ser Ser Ser Gly Arg Thr Ile
 1   5

<210> 279
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 279
gcgagacctt cgagtataga gactctgtta cggaatcagt accactacgg tgtggacgtc 60

<210> 280
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 280
Ala Arg Pro Ser Ser Ile Glu Thr Leu Leu Arg Asn Gln Tyr His Tyr
 1   5   10   15
Gly Val Asp Val
            20

<210> 281
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 281
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccgtca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300
caagggacac gactggagat taaa   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 Ser Ile Ser Ser Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85   90   95
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 283
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 283
cagagcatta gcagctat   18

<210> 284
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 284
Gln Ser Ile Ser Ser Tyr
 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> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 287
caacagagtt acagtacccc tccgatcacc 30

<210> 288
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 288
Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
 1   5   10

<210> 289
<211> 384
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 289
gaggtgcagc tggtggagtc tgggggaggc ttggcacagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agtcatgaaa tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtcgta gtggtagaat cataaactac 180
gcagactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagagagaga 300
ggctcgtatt acgatatttt gactggttcc caggactacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

<210> 290
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 290
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ala Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
            20   25   30
Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Tyr Ile Ser Arg Ser Gly Arg Ile Ile Asn Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Arg Gly Ser Tyr Tyr Asp Ile Leu Thr Gly Ser Gln Asp
            100   105   110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120   125

<210> 291
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 291
ggattcacct tcagtagtca tgaa   24

<210> 292
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 292
Gly Phe Thr Phe Ser Ser His Glu
 1   5

<210> 293
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 293
attagtcgta gtggtagaat cata   24

<210> 294
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

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

<210> 295
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 295
gcgagagaga gaggctcgta ttacgatatt ttgactggtt cccaggacta cggtatggac 60
gtc   63

<210> 296
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 296
Ala Arg Glu Arg Gly Ser Tyr Tyr Asp Ile Leu Thr Gly Ser Gln Asp
 1   5   10   15
Tyr Gly Met Asp Val
            20

<210> 297
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 297
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gaccattagc acctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300
caagggacac gactggagat taaa   324

<210> 298
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 298
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 Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85   90   95
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 299
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 299
cagaccatta gcacctat   18

<210> 300
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 300
Gln Thr Ile Ser Thr Tyr
 1   5

<210> 301
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 301
gctgcatcc   9

<210> 302
<211> 3
<212> PRT
<213> Artificial Sequence

<220>

<223> synthetic

<400> 302
Ala Ala Ser
 1

<210> 303
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 303
caacagagtt acagtacccc tccgatcacc 30

<210> 304
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 304
Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr
 1   5   10

<210> 305
<211> 381
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 305
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agttatgaaa tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtagtac caaatactac 180
gcagactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagaccttcg 300
agtataccag ctctgttacg gaaccagtac cactacggta tggacgtctg gggccaaggg 360
accacggtca ccgtctcctc a 381

<210> 306
<211> 127
<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 Gly
 1   5   10   15

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


<210> 307
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 307
ggattcacct tcagtagtta tgaa                                          24

<210> 308
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 308
Gly Phe Thr Phe Ser Ser Tyr Glu
 1               5


<210> 309
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 309
attagtagta gtggtagtac caaa                                          24

<210> 310
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic
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<400> 310
Ile Ser Ser Ser Gly Ser Thr Lys
 1   5

<210> 311
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 311
gcgagacctt cgagtatacc agctctgtta cggaaccagt accactacgg tatggacgtc 60

<210> 312
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 312
Ala Arg Pro Ser Ser Ile Pro Ala Leu Leu Arg Asn Gln Tyr His Tyr
 1   5   10   15
Gly Met Asp Val
            20

<210> 313
<211> 2051
<212> DNA
<213> Ebola virus

<400> 313
gaattcgcca ccatgggcgt gaccggcatc ctgcagctgc cccgggacag attcaagcgg 60
accagcttct tcctgtgggt catcatcctg ttccagcgga ccttcagcat ccccctgggc 120
gtgatccaca acagcaccct gcaggtgtcc gacgtggaca agctcgtgtg ccgggacaag 180
ctgagcagca ccaaccagct gagaagcgtg ggcctgaacc tggaaggcaa tggcgtggcc 240
accgatgtgc ctagcgccac caagagatgg ggcttcagat ccggcgtgcc ccccaaggtc 300
gtgaattatg aggccggcga gtgggccgag aactgctaca acctggaaat caagaagccc 360
gacggcagcg agtgcctgcc tgctgccccc gatggcatca gaggcttccc ccggtgcaga 420
tacgtgcaca aggtgtccgg cacaggcccc tgcgctggcg atttcgcctt tcacaaagag 480
ggcgcctttt tcctgtacga ccggctggcc tccaccgtga tctacagagg caccaccttt 540
gccgagggcg tggtggcctt tctgatcctg cctcaggcca agaaggactt cttcagcagc 600
cacccccctgc gcgagcctgt gaatgccaca gaggatccca gcagcggcta ctacagcacc 660
accatcagat accaggccac cggcttcggc accaacgaga cagagtacct gttcgaggtg 720
gacaacctga cctacgtgca gctggaaagc cggttcaccc cccagtttct gctgcagctg 780
aacgagacaa tctacgccag cggcaagcgg agcaacacca ccggcaagct gatctggaaa 840
gtgaaccccg agatcgatac cacaatcgga gagtgggcct tctgggagac aaagaagaac 900
ctgacccgga agatcagaag cgaggaactg agcttcaccg ccgtgtccaa cggccccaag 960
aacatcagcg gacagagccc cgccagaacc agcagcgacc ccgagacaaa caccaccaat 1020
gaggaccaca agatcatggc cagcgagaac agcagcgcca tggtgcaggt gcacagccag 1080
ggaagaaagg ccgctgtgtc ccacctgacc accctggcca caatctccac cagccctcag 1140
agcctgacca caaagcctgg ccccgacaac tccacccaca acacccccgt gtacaagctg 1200
gacatcagcg aggccacaca agtgggccag caccacagaa gggccgacaa cgatagcacc 1260

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gccagcgata cccctccagc cacaactgct gccggacctc tgaaggccga gaataccaac 1320
accagcaaga gcgccgacag cctggatctg gccaccacca caagccccca gaactactct 1380
gagacagccg gcaacaacaa cacccaccac caggataccg gcgaggaaag cgccagctct 1440
ggcaagctgg gactgatcac caacacaatc gccggcgtgg ccggcctgat taccgggggg 1500
agaagaacca gacgggaagt gatcgtgaac gcccagccca agtgcaaccc caacctgcac 1560
tactggacca cccaggatga gggcgctgct atcggactgg cctggatccc ttactttggc 1620
cctgccgccg agggcatcta caccgaggga ctgatgcaca accaggacgg cctgatctgc 1680
ggactgaggc agctggccaa cgaaaccaca caggctctgc agctgttcct gagagccacc 1740
accgagctga ggaccttctc catcctgaac agaaaggcta tcgacttcct gctgcagcgc 1800
tggggcggca cctgtcacat tctgggccct gactgctgca tcgagcccca cgactggacc 1860
aagaatatca ccgacaagat cgaccagatc atccacgact ttgtggacaa gaccctgccc 1920
gaccagggcg acaatgacaa ctggtggaca ggctggcggc agtggattcc tgccggcatt 1980
ggagtgaccg gcgtgatcat tgccgtgatc gccctgttct gcatctgcaa gttcgtgttc 2040
tgagcggccg c                                                      2051
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<210> 314
<211> 676
<212> PRT
<213> Ebola virus

<400> 314

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

```
Glu Leu Ser Phe Thr Ala Val Ser Asn Gly Pro Lys Asn Ile Ser Gly
305                 310                 315                 320
Gln Ser Pro Ala Arg Thr Ser Ser Asp Pro Glu Thr Asn Thr Thr Asn
                325                 330                 335
Glu Asp His Lys Ile Met Ala Ser Glu Asn Ser Ser Ala Met Val Gln
            340                 345                 350
Val His Ser Gln Gly Arg Lys Ala Ala Val Ser His Leu Thr Thr Leu
        355                 360                 365
Ala Thr Ile Ser Thr Ser Pro Gln Pro Pro Thr Thr Lys Thr Gly Pro
    370                 375                 380
Asp Asn Ser Thr His Asn Thr Pro Val Tyr Lys Leu Asp Ile Ser Glu
385                 390                 395                 400
Ala Thr Gln Val Gly Gln His His Arg Arg Ala Asp Asn Asp Ser Thr
                405                 410                 415
Ala Ser Asp Thr Pro Pro Ala Thr Thr Ala Ala Gly Pro Leu Lys Ala
            420                 425                 430
Glu Asn Thr Asn Thr Ser Lys Ser Ala Asp Ser Leu Asp Leu Ala Thr
        435                 440                 445
Thr Thr Ser Pro Gln Asn Tyr Ser Glu Thr Ala Gly Asn Asn Asn Thr
    450                 455                 460
His His Gln Asp Thr Gly Glu Glu Ser Ala Ser Ser Gly Lys Leu Gly
465                 470                 475                 480
Leu Ile Thr Asn Thr Ile Ala Gly Val Ala Gly Leu Ile Thr Gly Gly
                485                 490                 495
Arg Arg Thr Arg Arg Glu Val Ile Val Asn Ala Gln Pro Lys Cys Asn
            500                 505                 510
Pro Asn Leu His Tyr Trp Thr Thr Gln Asp Glu Gly Ala Ala Ile Gly
        515                 520                 525
Leu Ala Trp Ile Pro Tyr Phe Gly Pro Ala Ala Glu Gly Ile Tyr Thr
    530                 535                 540
Glu Gly Leu Met His Asn Gln Asp Gly Leu Ile Cys Gly Leu Arg Gln
545                 550                 555                 560
Leu Ala Asn Glu Thr Thr Gln Ala Leu Gln Leu Phe Leu Arg Ala Thr
                565                 570                 575
Thr Glu Leu Arg Thr Phe Ser Ile Leu Asn Arg Lys Ala Ile Asp Phe
            580                 585                 590
Leu Leu Gln Arg Trp Gly Gly Thr Cys His Ile Leu Gly Pro Asp Cys
        595                 600                 605
Cys Ile Glu Pro His Asp Trp Thr Lys Asn Ile Thr Asp Lys Ile Asp
    610                 615                 620
Gln Ile Ile His Asp Phe Val Asp Lys Thr Leu Pro Asp Gln Gly Asp
625                 630                 635                 640
Asn Asp Asn Trp Trp Thr Gly Trp Arg Gln Trp Ile Pro Ala Gly Ile
                645                 650                 655
Gly Val Thr Gly Val Ile Ile Ala Val Ile Ala Leu Phe Cys Ile Cys
            660                 665                 670
Lys Phe Val Phe
        675
```

<210> 315
<211> 676
<212> PRT
<213> Ebola virus

<400> 315

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Met Gly Val Thr Gly Ile Leu Gln Leu Pro Arg Asp Arg Phe Lys Arg
 1               5                  10                  15
Thr Ser Phe Phe Leu Trp Val Ile Ile Leu Phe Gln Arg Thr Phe Ser
```

```
            20                  25                  30
Ile Pro Leu Gly Val Ile His Asn Ser Thr Leu Gln Val Ser Asp Val
        35                  40                  45
Asp Lys Leu Val Cys Arg Asp Lys Leu Ser Ser Thr Asn Gln Leu Arg
    50                  55                  60
Ser Val Gly Leu Asn Leu Glu Gly Asn Gly Val Ala Thr Asp Val Pro
65                  70                  75                  80
Ser Ala Thr Lys Arg Trp Gly Phe Arg Ser Gly Val Pro Pro Lys Val
                85                  90                  95
Val Asn Tyr Glu Ala Gly Glu Trp Ala Glu Asn Cys Tyr Asn Leu Glu
            100                 105                 110
Ile Lys Lys Pro Asp Gly Ser Glu Cys Leu Pro Ala Ala Pro Asp Gly
        115                 120                 125
Ile Arg Gly Phe Pro Arg Cys Arg Tyr Val His Lys Val Ser Gly Thr
    130                 135                 140
Gly Pro Cys Ala Gly Asp Phe Ala Phe His Lys Glu Gly Ala Phe Phe
145                 150                 155                 160
Leu Tyr Asp Arg Leu Ala Ser Thr Val Ile Tyr Arg Gly Thr Thr Phe
                165                 170                 175
Ala Glu Gly Val Val Ala Phe Leu Ile Leu Pro Gln Ala Lys Lys Asp
            180                 185                 190
Phe Phe Ser Ser His Pro Leu Arg Glu Pro Val Asn Ala Thr Glu Asp
        195                 200                 205
Pro Ser Ser Gly Tyr Tyr Ser Thr Thr Ile Arg Tyr Gln Ala Thr Gly
    210                 215                 220
Phe Gly Thr Asn Glu Thr Glu Tyr Leu Phe Glu Val Asp Asn Leu Thr
225                 230                 235                 240
Tyr Val Gln Leu Glu Ser Arg Phe Thr Pro Gln Phe Leu Leu Gln Leu
                245                 250                 255
Asn Glu Thr Ile Tyr Ala Ser Gly Lys Arg Ser Asn Thr Thr Gly Lys
            260                 265                 270
Leu Ile Trp Lys Val Asn Pro Glu Ile Asp Thr Thr Ile Gly Glu Trp
        275                 280                 285
Ala Phe Trp Glu Thr Lys Lys Asn Leu Thr Arg Lys Ile Arg Ser Glu
    290                 295                 300
Glu Leu Ser Phe Thr Ala Val Ser Asn Gly Pro Lys Asn Ile Ser Gly
305                 310                 315                 320
Gln Ser Pro Ala Arg Thr Ser Ser Asp Pro Glu Thr Asn Thr Thr Asn
                325                 330                 335
Glu Asp His Lys Ile Met Ala Ser Glu Asn Ser Ser Ala Met Val Gln
            340                 345                 350
Val His Ser Gln Gly Arg Lys Ala Ala Val Ser His Leu Thr Thr Leu
        355                 360                 365
Ala Thr Ile Ser Thr Ser Pro Gln Pro Pro Thr Thr Lys Thr Gly Pro
    370                 375                 380
Asp Asn Ser Thr His Asn Thr Pro Val Tyr Lys Leu Asp Ile Ser Glu
385                 390                 395                 400
Ala Thr Gln Val Gly Gln His His Arg Arg Ala Asp Asn Asp Ser Thr
                405                 410                 415
Ala Ser Asp Thr Pro Pro Ala Thr Thr Ala Ala Gly Pro Leu Lys Ala
            420                 425                 430
Glu Asn Thr Asn Thr Ser Lys Ser Ala Asp Ser Leu Asp Leu Ala Thr
        435                 440                 445
Thr Thr Ser Pro Gln Asn Tyr Ser Glu Thr Ala Gly Asn Asn Asn Thr
    450                 455                 460
His His Gln Asp Thr Gly Glu Glu Ser Ala Ser Ser Gly Lys Leu Gly
465                 470                 475                 480
Leu Ile Thr Asn Thr Ile Ala Gly Val Ala Gly Leu Ile Thr Gly Gly
                485                 490                 495
```

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Arg Arg Thr Arg Arg Glu Val Ile Val Asn Ala Gln Pro Lys Cys Asn
            500                 505                 510
Pro Asn Leu His Tyr Trp Thr Thr Gln Asp Glu Gly Ala Ala Ile Gly
        515                 520                 525
Leu Ala Trp Ile Pro Tyr Phe Gly Pro Ala Ala Glu Gly Ile Tyr Thr
    530                 535                 540
Glu Gly Leu Met His Asn Gln Asp Gly Leu Ile Cys Gly Leu Arg Gln
545                 550                 555                 560
Leu Ala Asn Glu Thr Thr Gln Ala Leu Gln Leu Phe Leu Arg Ala Thr
                565                 570                 575
Thr Glu Leu Arg Thr Phe Ser Ile Leu Asn Arg Lys Ala Ile Asp Phe
            580                 585                 590
Leu Leu Gln Arg Trp Gly Gly Thr Cys His Ile Leu Gly Pro Asp Cys
        595                 600                 605
Cys Ile Glu Pro His Asp Trp Thr Lys Asn Ile Thr Asp Lys Ile Asp
    610                 615                 620
Gln Ile Ile His Asp Phe Val Asp Lys Thr Leu Pro Asp Gln Gly Asp
625                 630                 635                 640
Asn Asp Asn Trp Trp Thr Gly Trp Arg Gln Trp Ile Pro Ala Gly Ile
                645                 650                 655
Gly Val Thr Gly Val Ile Ile Ala Val Ile Ala Leu Phe Cys Ile Cys
            660                 665                 670
Lys Phe Val Phe
        675


<210> 316
<211> 364
<212> PRT
<213> Ebola virus

<400> 316
Met Gly Val Thr Gly Ile Leu Gln Leu Pro Arg Asp Arg Phe Lys Arg
 1                5                  10                  15
Thr Ser Phe Phe Leu Trp Val Ile Ile Leu Phe Gln Arg Thr Phe Ser
            20                  25                  30
Ile Pro Leu Gly Val Ile His Asn Ser Thr Leu Gln Val Ser Asp Val
        35                  40                  45
Asp Lys Leu Val Cys Arg Asp Lys Leu Ser Ser Thr Asn Gln Leu Arg
    50                  55                  60
Ser Val Gly Leu Asn Leu Glu Gly Asn Gly Val Ala Thr Asp Val Pro
65                  70                  75                  80
Ser Ala Thr Lys Arg Trp Gly Phe Arg Ser Gly Val Pro Pro Lys Val
                85                  90                  95
Val Asn Tyr Glu Ala Gly Glu Trp Ala Glu Asn Cys Tyr Asn Leu Glu
            100                 105                 110
Ile Lys Lys Pro Asp Gly Ser Glu Cys Leu Pro Ala Ala Pro Asp Gly
        115                 120                 125
Ile Arg Gly Phe Pro Arg Cys Arg Tyr Val His Lys Val Ser Gly Thr
    130                 135                 140
Gly Pro Cys Ala Gly Asp Phe Ala Phe His Lys Glu Gly Ala Phe Phe
145                 150                 155                 160
Leu Tyr Asp Arg Leu Ala Ser Thr Val Ile Tyr Arg Gly Thr Thr Phe
                165                 170                 175
Ala Glu Gly Val Val Ala Phe Leu Ile Leu Pro Gln Ala Lys Lys Asp
            180                 185                 190
Phe Phe Ser Ser His Pro Leu Arg Glu Pro Val Asn Ala Thr Glu Asp
        195                 200                 205
Pro Ser Ser Gly Tyr Tyr Ser Thr Thr Ile Arg Tyr Gln Ala Thr Gly
```

```
    210                 215                 220
Phe Gly Thr Asn Glu Thr Glu Tyr Leu Phe Glu Val Asp Asn Leu Thr
225                 230                 235                 240
Tyr Val Gln Leu Glu Ser Arg Phe Thr Pro Gln Phe Leu Leu Gln Leu
                245                 250                 255
Asn Glu Thr Ile Tyr Ala Ser Gly Lys Arg Ser Asn Thr Thr Gly Lys
            260                 265                 270
Leu Ile Trp Lys Val Asn Pro Glu Ile Asp Thr Thr Ile Gly Glu Trp
        275                 280                 285
Ala Phe Trp Glu Thr Lys Lys Thr Ser Leu Glu Lys Phe Ala Val Lys
    290                 295                 300
Ser Cys Leu Ser Gln Leu Tyr Gln Thr Asp Pro Lys Thr Ser Val Val
305                 310                 315                 320
Arg Val Arg Arg Glu Leu Leu Pro Thr Gln Arg Pro Thr Gln Gln Met
                325                 330                 335
Lys Thr Thr Lys Ser Trp Leu Gln Lys Ile Pro Leu Gln Trp Phe Lys
            340                 345                 350
Cys Thr Val Lys Glu Gly Lys Leu Gln Cys Arg Ile
        355                 360
```

<210> 317
<211> 360
<212> PRT
<213> Artificial Sequence

<220>
<223> aa 1-332: Zaire_Ebola_GP aa 33 through 364 of AHX24650
aa 333-360: myc-myc-hexahistidine tag

<400> 317

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

```
Tyr Val Gln Leu Glu Ser Arg Phe Thr Pro Gln Phe Leu Leu Gln Leu
    210                 215                 220
Asn Glu Thr Ile Tyr Ala Ser Gly Lys Arg Ser Asn Thr Thr Gly Lys
225                 230                 235                 240
Leu Ile Trp Lys Val Asn Pro Glu Ile Asp Thr Thr Ile Gly Glu Trp
                245                 250                 255
Ala Phe Trp Glu Thr Lys Lys Thr Ser Leu Glu Lys Phe Ala Val Lys
            260                 265                 270
Ser Cys Leu Ser Gln Leu Tyr Gln Thr Asp Pro Lys Thr Ser Val Val
        275                 280                 285
Arg Val Arg Arg Glu Leu Leu Pro Thr Gln Arg Pro Thr Gln Gln Met
    290                 295                 300
Lys Thr Thr Lys Ser Trp Leu Gln Lys Ile Pro Leu Gln Trp Phe Lys
305                 310                 315                 320
Cys Thr Val Lys Glu Gly Lys Leu Gln Cys Arg Ile Glu Gln Lys Leu
                325                 330                 335
Ile Ser Glu Glu Asp Leu Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu
            340                 345                 350
Asp Leu His His His His His His
        355                 360
```

<210> 318
<211> 628
<212> PRT
<213> Artificial Sequence

<220>
<223> aa 1-618: Zaire ebolavirus (strain H.sapiens-wt/GIN/2014/Kissidougou-C15) GP (aa 33 through 650 (AHX24649.1))
aa 619-628: decahistidine tag

<400> 318

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

```
Phe Gly Thr Asn Glu Thr Glu Tyr Leu Phe Glu Val Asp Asn Leu Thr
        195                 200                 205
Tyr Val Gln Leu Glu Ser Arg Phe Thr Pro Gln Phe Leu Leu Gln Leu
    210                 215                 220
Asn Glu Thr Ile Tyr Thr Ser Gly Lys Arg Ser Asn Thr Thr Gly Lys
225                 230                 235                 240
Leu Ile Trp Lys Val Asn Pro Glu Ile Asp Thr Thr Ile Gly Glu Trp
                245                 250                 255
Ala Phe Trp Glu Thr Lys Lys Asn Leu Thr Arg Lys Ile Arg Ser Glu
            260                 265                 270
Glu Leu Ser Phe Thr Val Val Ser Asn Gly Ala Lys Asn Ile Ser Gly
        275                 280                 285
Gln Ser Pro Ala Arg Thr Ser Ser Asp Pro Gly Thr Asn Thr Thr Thr
    290                 295                 300
Glu Asp His Lys Ile Met Ala Ser Glu Asn Ser Ser Ala Met Val Gln
305                 310                 315                 320
Val His Ser Gln Gly Arg Glu Ala Ala Val Ser His Leu Thr Thr Leu
                325                 330                 335
Ala Thr Ile Ser Thr Ser Pro Gln Ser Leu Thr Thr Lys Pro Gly Pro
            340                 345                 350
Asp Asn Ser Thr His Asn Thr Pro Val Tyr Lys Leu Asp Ile Ser Glu
        355                 360                 365
Ala Thr Gln Val Glu Gln His His Arg Arg Thr Asp Asn Asp Ser Thr
    370                 375                 380
Ala Ser Asp Thr Pro Ser Ala Thr Thr Ala Ala Gly Pro Pro Lys Ala
385                 390                 395                 400
Glu Asn Thr Asn Thr Ser Lys Ser Thr Asp Phe Leu Asp Pro Ala Thr
                405                 410                 415
Thr Thr Ser Pro Gln Asn His Ser Glu Thr Ala Gly Asn Asn Asn Thr
            420                 425                 430
His His Gln Asp Thr Gly Glu Glu Ser Ala Ser Ser Gly Lys Leu Gly
        435                 440                 445
Leu Ile Thr Asn Thr Ile Ala Gly Val Ala Gly Leu Ile Thr Gly Gly
    450                 455                 460
Arg Arg Thr Arg Arg Glu Ala Ile Val Asn Ala Gln Pro Lys Cys Asn
465                 470                 475                 480
Pro Asn Leu His Tyr Trp Thr Thr Gln Asp Glu Gly Ala Ala Ile Gly
                485                 490                 495
Leu Ala Trp Ile Pro Tyr Phe Gly Pro Ala Ala Glu Gly Ile Tyr Ile
            500                 505                 510
Glu Gly Leu Met His Asn Gln Asp Gly Leu Ile Cys Gly Leu Arg Gln
        515                 520                 525
Leu Ala Asn Glu Thr Thr Gln Ala Leu Gln Leu Phe Leu Arg Ala Thr
    530                 535                 540
Thr Glu Leu Arg Thr Phe Ser Ile Leu Asn Arg Lys Ala Ile Asp Phe
545                 550                 555                 560
Leu Leu Gln Arg Trp Gly Gly Thr Cys His Ile Leu Gly Pro Asp Cys
                565                 570                 575
Cys Ile Glu Pro His Asp Trp Thr Lys Asn Ile Thr Asp Lys Ile Asp
            580                 585                 590
Gln Ile Ile His Asp Phe Val Asp Lys Thr Leu Pro Asp Gln Gly Asp
        595                 600                 605
Asn Asp Asn Trp Trp Thr Gly Trp Arg Gln His His His His His His
    610                 615                 620
His His His His
625
```