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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 July 2008 (17.07.2008)

PCT

(10) International Publication Number
WO 2008/085878 A2

(51) International Patent Classification:
C07K 16/00 (2006.01)

(21) International Application Number:
PCT/US2008/000104

(22) International Filing Date: 3 January 2008 (03.01.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/883,271	3 January 2007 (03.01.2007)	US
60/888,405	6 February 2007 (06.02.2007)	US

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(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, BR, BW, BY, BZ, CA, CH, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

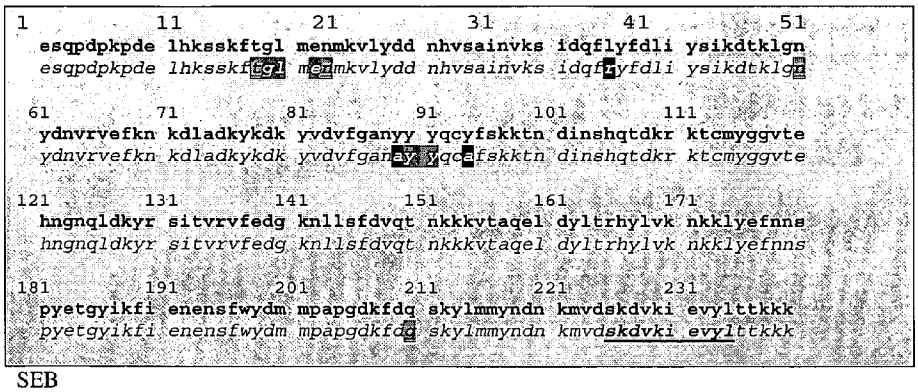
Published:

— *without international search report and to be republished upon receipt of that report*

— *with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description*

[Continued on next page]

(54) Title: HIGH AFFINITY ANTIBODIES THAT NEUTRALIZE STAPHYLCOCCUS ENTEROTOXIN B



SEB
SEB mutein vaccine
IVIG binding epitopes
TCR-binding H-bonds
TCR-binding Van der Waals contacts

(57) Abstract: This invention provides antibodies that specifically bind and neutralize Staphylococcus enterotoxin B. In addition, nucleic acids encoding such antibodies, and cells that express such antibodies are provided. Also provided are methods for treating diseases mediated by, and for neutralizing Staphylococcus enterotoxin B.

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— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

HIGH AFFINITY ANTIBODIES THAT NEUTRALIZE STAPHYLOCOCCUS ENTEROTOXIN B

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/883,271, filed January 3, 2007, and of U.S. Provisional Application No. 60/888,405, filed February 6, 2007, both of which are incorporated by reference herein.

REFERENCE TO GOVERNMENT CONTRACT

[0002] Portions of the disclosure herein may have been supported in part by contracts from the National Institutes of Health, Contract No. U01AI075399. The United States Government may have certain rights in this application.

FIELD

[0003] The invention relates generally to the field of immunotherapeutics. More specifically, the invention relates to monoclonal antibodies that can neutralize bacterial toxins, and methods for using such antibodies to treat subjects exposed to such toxins.

BACKGROUND

[0004] Bioterrorism threats have received a great deal of attention at present because of the ease of use of many of these deadly agents as well as accessibility of a largely unprotected populace. There can be significant economic and political ramifications that follow a bioterrorism attack, as was seen in the attacks with anthrax-laden envelopes in Washington, D.C. and New York in 2001 that resulted in disruption of postal service and 18 deaths. Due to the

threat from such agents, the Centers for Disease Control established a list of biological agents that can be "weaponized" and have the potential to cause large scale morbidity and mortality. These select agents have been classified into three groups (A, B, and C) based on their potential for wide dissemination in civilian populations. Category B agents are considered to be moderately easy to disseminate and would, if distributed into civilian populations, result in moderate morbidity and mortality. Among the list of Category B agents is the Staphylococcal enterotoxin B (SEB) produced by the microorganism *Staphylococcus aureus* (Mantis, NJ (2005) Adv. Drug Del. Rev. 57:1424-39). SEB has the potential to cause disease in humans at relatively low doses, in particular when the route of administration occurs by a mucosal surface. Typical routes of administration for SEB are by inhalation as an aerosol or by ingestion of SEB-laden food or water.

[0005] There are at least seven antigenically distinct enterotoxins secreted by strains of *S. aureus* (Kotb (1998) Curr. Opin. Microbiol 1:56-65; Bergdoll (1983) Enterotoxins, in: C.S.F. Easmon, C. Adlam (Eds.), Staphylococcus and Staphylococcal Infections, Academic Press, New York, New York, pp. 559-598). SEB is a single polypeptide of approximately 28,000 Da molecular mass, and is comprised of two tightly packed domains: a large domain and a small domain (Swaminathan *et al.* (1992) Nature 359:801-6). Due to the compact tertiary structure of SEB, it is highly resistant to degradation by proteases, including trypsin, chymotrypsin, and papain. It is likely that protease resistance contributes to SEB stability in the intestinal lumen (Mantis (2005)).

[0006] Infection of a host organism by pathogenic bacteria such as staphylococci is aided by the production of exotoxins. The SEB produced by *S. aureus* is a protein that is classified as a superantigen (SAg). Superantigens are defined as toxins that can activate T cells by forming a bridge between a MHC II on antigen presenting cells (APCs) and the T cell receptors (TCR) on specific subsets of $CD4^+$ and $CD8^+$ T cells. SEB recognizes one of the seven classes of human V_β^+ T cell receptors: V_β 3, 12, 13.2, 14, 15, 17, 20 (Jardetzky *et al.* (1994) Nature 368:711-8; Leder *et al.* (1998) J. Exp. Med. 187:823-33; Li *et al.* (1998) Immunity 9:807-16). As a consequence of SEB binding, T cells release massive quantities of cytokines including IL-2, TNF-β, and interferon-γ, and undergo hyper-proliferation that ultimately results in their depletion (Kappler *et al.* (1989) Science 244:811-3). MHC II^+ APCs respond by producing TNF-α and IL-1 (Krakauer (2003) Methods Mol. Biol. 214:137-49). Two regions of SEB are involved in the interaction with MHC II, including a hydrophobic pocket near L45 and a polar pocket that includes residues Y89, Y115, and E67 (Mantis (2005); Jardetzky *et al.* (1994); Olson *et al*, (1997) J. Mol. Recognit. 10:277-89; and, Seth *et al.* (1994) Nature 369:324-7). It is

predicted that obtaining a greater understanding of the molecular interactions between SEB and TCR-MHC II will lead to the development of attenuated SEB vaccine candidates; this prediction has been realized to some extent (Ulrich *et al.* (1998) Vaccine 16:1857-64).

[0007] SEB is a fairly stable protein, although it can be denatured by prolonged boiling. Because it is stable as an aerosol, it is considered a likely candidate for use as a bioterrorist agent. It is an incapacitating toxin, with an LD_{50} (the dose lethal to 50% of the population) by inhalation of 27 μg/kg, and an ID_{50} (the dose infectious to 50% of the population) of only 0.0004 μg/kg. SEB most commonly enters the body by either ingestion or inhalation, thereby leading to two different clinical presentations of SEB food poisoning and SEB respiratory syndrome. On the battlefield it is unlikely that SEB will be ingested, but both routes are possible in a terrorist attack. SEB as a terrorist weapon of mass destruction would most likely be disseminated as an aerosol. (Madsen (2001) Clinics in Laboratory Medicine 21:593-605).

[0008] SEB food poisoning is characterized by severe abdominal cramps and usually non-bloody diarrhea, sometimes accompanied by a headache and fever. Symptoms begin suddenly, usually within 2 to 8 hours after ingestion and usually abate in 12 hours or less. Inhalation of aerosolized preformed toxin produces SEB respiratory syndrome, which is characterized by fever, headache, chills, myalagias, nonproductive cough, dyspnea, and retrosternal chest pain. Inadvertent swallowing of the toxin leads to nausea and vomiting, and eye contact may induce conjunctival injection. Fever of 39°C to 41°C may last up to 5 days, and cough may persist up to 4 weeks. The mechanism of death in fatal inhalation cases is pulmonary edema (Madsen 2001).

[0009] Several potential strategies are under development for the treatment of SEB-infected individuals, although no effective treatment currently exists. The use of intravenous immunoglobulins has been an approach that has met with limited success (Darrenberg *et al.* (2004) Clin. Infect. Dis. 38:836-42). Another approach under development has recently been reported in a mouse SEB model system (Krakauer *et al.* (2006) Antimicrob. Agents Chemother. 50:391-5). In mouse SEB model system, mice were exposed to SEB and treated with the anti-inflammatory drug dexamethasone. In an LPS-potentiated model of SEB, toxic shock can be halted if the drug is administered to the mice quickly following SEB treatment (short treatment window). As a practical matter, however, it would be difficult to correctly diagnose exposure to SEB and administer sufficient dexamethasone to quell the SEB-mediated diseases within such a short treatment window.

[0010] SEB vaccine research has been primarily carried out by the United States Army Medical Research Institute of Infectious Diseases (USAMRIID). The vaccine development has

focused on the use of formalin-inactivated toxin (Tseng *et al.* (1995) Infect. Immun. 63:2880-5). The toxoid vaccine is typically made by prolonged incubation in formalin at pH 7.5. Although the SEB toxoid vaccine was immunogenic and patients did develop an immune reaction to SEB, this vaccine was largely abandoned by USAMRIID in recent years and supplanted by recombinant, site-directed attenuated mutants (Stiles *et al.* (2001) Infect. Immun. 69:2031-6). Unfortunately, these mutants may not be suitable for use in humans due to retention of emetic activity in primate studies (Harris *et al.* (1993) Infect. Immun. 61:3175-83).

[0011] The SEB work reviewed above suggests that effective methods for combating a terrorist's use of SEB are currently lacking. Therefore, an approach to develop a drug that can neutralize the activity of SEB *in vivo* would be a valuable human therapeutic for the treatment and prevention of SEB-mediated disease.

SUMMARY

[0012] The invention features isolated human antibodies and antigen-binding fragments that specifically bind to, and preferably neutralize Staphylococcus enterotoxin B. The antibodies and antigen-binding fragments can comprise a heavy chain CDR3 having SEQ ID NO: 39, 40, 70, 94, 118, 132, or 148. The antibodies and antigen-binding fragments can comprise heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 68, 69, and 70; SEQ ID NOs: 130, 131, and 132; SEQ ID NOs: 92, 93, and 94; or SEQ ID NOs: 144, 146, and 148. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a heavy chain variable domain of SEQ ID NO: 160, 176, 204, or 230. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a heavy chain having SEQ ID NO: 30, 34, 126, 142, 216, 232, or 251.

[0013] In some preferred embodiments, the antibodies and antigen-binding fragments can comprise light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 56, 57, and 58; SEQ ID NOs: 104, 105, and 106; SEQ ID NOs: 80, 81, and 82; or SEQ ID NOs: 136, 138, and 140. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a light chain variable domain of SEQ ID NO: 158, 174, 200, or 228. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a light chain having SEQ ID NO: 28, 32, 36, 134, 186, 214, or 249.

[0014] In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a heavy chain having CDR1 of SEQ ID NO: 68, 92, 130, or 144; CDR2 of SEQ ID NO: 69, 93, 131, or 146; and CDR3 of SEQ ID NO: 70, 94, 132, or 148; and a light chain having CDR1 of SEQ ID NO: 56, 80, 104, or 136; CDR2 of SEQ ID NO: 57, 81, 105, or 138; and CDR3 of SEQ ID NO: 58, 82, 106, or 140. In some preferred embodiments, the antibodies and

antigen-binding fragments can comprise a heavy chain variable domain having SEQ ID NO: 160, 176, 204, or 230 and a light chain variable domain having SEQ ID NO: 158, 174, 200, or 228.

[0015] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 68, CDR2 of SEQ ID NO: 69, and CDR3 of SEQ ID NO: 70 and a light chain having CDR1 of SEQ ID NO: 56, CDR2 of SEQ ID NO: 57, and CDR3 of SEQ ID NO: 58. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 176 and a light chain having a variable domain of SEQ ID NO: 174. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 30 and a light chain having SEQ ID NO: 28.

[0016] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 130, CDR2 of SEQ ID NO: 131, and CDR3 of SEQ ID NO: 132, and a light chain having CDR1 of SEQ ID NO: 104, CDR2 of SEQ ID NO: 105, and CDR3 of SEQ ID NO: 106. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 204 and a light chain having a variable domain of SEQ ID NO: 200. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 232 and a light chain having SEQ ID NO: 186.

[0017] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 92, CDR2 of SEQ ID NO: 93, and CDR3 of SEQ ID NO: 94, and a light chain having CDR1 of SEQ ID NO: 80, CDR2 of SEQ ID NO: 81, and CDR3 of SEQ ID NO: 82. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 160 and a light chain having a variable domain of SEQ ID NO: 158. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 251 and a light chain having SEQ ID NO: 249.

[0018] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 144, CDR2 of SEQ ID NO: 146, and CDR3 of SEQ ID NO: 148, and a light chain having CDR1 of SEQ ID NO: 136, CDR2 of SEQ ID NO: 138, and CDR3 of SEQ ID NO: 140. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 230 and a light chain having a variable domain of SEQ ID NO: 228. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 216 and a light chain having SEQ ID NO: 214.

[0019] The present invention also contemplates antibodies, or antigen-binding fragments thereof, having amino acid sequences that are substantially the same as the previously described amino acid sequences. For example, such antibodies or antigen-binding fragments thereof may include those wherein the heavy chain CDR1, CDR2, and CDR3 are at least 90% identical to the amino acid sequences of SEQ ID NOs: 68, 69, and 70; 92, 93, and 94; 130, 131, and 132; or 144, 146, and 148, respectively. The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those wherein the light chain CDR1, CDR2, and CDR3 are at least 90% identical to the amino acid sequences of SEQ ID NOs: 56, 57, and 58; 80, 81, and 82; 104, 105, and 106; or 136, 138, and 140, respectively. In some embodiments, the antibodies or antigen binding-fragments having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those wherein the heavy chain CDR1, CDR2, and CDR3 are at least 90% identical to the amino acid sequences of SEQ ID NOs: 68, 69, and 70; 92, 93, and 94; 130, 131, and 132; or 144, 146, and 148, respectively, and wherein the light chain CDR1, CDR2, and CDR3 are at least 90% identical to the amino acid sequences of SEQ ID NOs: 56, 57, and 58; 80, 81, and 82; 104, 105, and 106; or 136, 138, and 140, respectively. The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those wherein the heavy chain CDR3 is at least 90% identical to the amino acid sequence of SEQ ID NO: 39, 40, 70, 94, 132, or 148. Such antibodies or antigen-binding fragments thereof may include those wherein the light chain CDR3 is at least 90% identical to the amino acid sequence of SEQ ID NO: 41, 42, 58, 82, 106, or 140.

[0019] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those wherein the heavy chain CDR1, CDR2, and CDR3 and the light chain CDR1, CDR2, and CDR3 are at least 90% identical to the antibody or antigen-binding fragment thereof with a heavy chain having CDR1 of SEQ ID NO: 68, CDR2 of SEQ ID NO: 69, and CDR3 of SEQ ID NO: 70 and a light chain having CDR1 of SEQ ID NO: 56, CDR2 of SEQ ID NO: 57, and CDR3 of SEQ ID NO: 58.

[0020] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those wherein the heavy chain CDR1, CDR2, and CDR3 and the light chain CDR1, CDR2, and CDR3 are at least 90% identical to the antibody or antigen-binding fragment thereof with a heavy chain having CDR1 of SEQ ID NO: 130, CDR2 of SEQ ID NO: 131, and CDR3 of

SEQ ID NO: 132, and a light chain having CDR1 of SEQ ID NO: 104, CDR2 of SEQ ID NO: 105, and CDR3 of SEQ ID NO: 106.

[0021] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those wherein the heavy chain CDR1, CDR2, and CDR3 and the light chain CDR1, CDR2, and CDR3 are at least 90% identical to the antibody or antigen-binding fragment thereof with a heavy chain having CDR1 of SEQ ID NO: 92, CDR2 of SEQ ID NO: 93, and CDR3 of SEQ ID NO: 94, and a light chain having CDR1 of SEQ ID NO: 80, CDR2 of SEQ ID NO: 81, and CDR3 of SEQ ID NO: 82.

[0022] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those wherein the heavy chain CDR1, CDR2, and CDR3 and the light chain CDR1, CDR2, and CDR3 are at least 90% identical to the antibody or antigen-binding fragment thereof with a heavy chain having CDR1 of SEQ ID NO: 144, CDR2 of SEQ ID NO: 146, and CDR3 of SEQ ID NO: 148, and a light chain having CDR1 of SEQ ID NO: 136, CDR2 of SEQ ID NO: 138, and CDR3 of SEQ ID NO: 140.

[0023] In a further example, antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain at least 90% identical to the amino acid sequence of SEQ ID NO: 176, 160, 204, or 230 and a light chain having a variable domain at least 90% identical to the amino acid sequence of SEQ ID NO: 174, 158, 200, or 228.

[0024] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those having a heavy chain having a variable domain and a light chain having a variable domain at least 90% identical to the amino acid sequence of SEQ ID NO: 176 and SEQ ID NO: 174.

[0025] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those having a heavy chain having a variable domain and a light chain having a variable domain at least 90% identical to the amino acid sequence of SEQ ID NO: 160 and SEQ ID NO: 158.

[0026] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those having a heavy chain having a variable domain and a light chain having a variable

domain at least 90% identical to the amino acid sequence of SEQ ID NO: 204 and SEQ ID NO: 200.

[0027] The antibodies or antigen-binding fragments thereof having amino acid sequences that are substantially the same as the previously described amino acid sequences may include those having a heavy chain having a variable domain and a light chain having a variable domain at least 90% identical to the amino acid sequence of SEQ ID NO: 230 and SEQ ID NO: 228.

[0028] The antibodies and antigen-binding fragments are high affinity antibodies and antigen-binding fragments, and can have an affinity of less than about 1 x 10^{-8} M, preferably less than about 2 x 10^{-8} M, and more preferably less than about 3 x 10^{-8} M. Preferably, the antibodies are monoclonal antibodies, and more preferably, are human monoclonal antibodies. Cells that express such antibodies and antigen-binding fragments, such as hybridoma cells and expression cells, are also provided.

[0029] The invention further contemplates antibodies, or antigen-binding fragments thereof, that compete for binding to SEB with antibody 79G9, 154G12, F10, 100C9, F6, E12 or C5.

[0030] The invention also contemplates antibodies, or antigen-binding fragments thereof, that bind the same epitope as antibody 79G9, 154G12, F10, 100C9, F6, E12 or C5.

[0031] The invention also features polynucleotides that encode antibodies and antigen-binding fragments that specifically bind to Staphylococcus enterotoxin B. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 68, 69, and 70, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 62, 63, and 64. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 130, 131, and 132, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 123 or 194, 124 or 196, and 125 or 198. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 92, 93, and 94, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 86 or 166, 87 or 168, and 88 or 170. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 144, 146, and 148, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 253 or 222, 255 or 224, and 257 or 226.

[0032] In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 56, 57, and 58, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 50, 51, and 52. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 104, 105, and 106, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 98 or 180, 99 or 182, and 100 or 184. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 80, 81, and 82, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 74 or 152, 75 or 154, and 76 or 156. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 136, 138, and 140, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 259 or 208, 261 or 210, and 263 or 212.

[0033] In some preferred embodiments, the antibody or antigen-binding fragment heavy chain variable domain is encoded by a polynucleotide comprising SEQ ID NO: 159, 164, 172, 175, 192, 203, or 229. In some preferred embodiments, the heavy chain sequence is encoded by a polynucleotide comprising SEQ ID NO: 29, 33, 119, 141, 162, 163, 190, 191, 215, 218, 219, 231, or 250. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 160. For example, the polynucleotide may comprise SEQ ID NO: 159 or 164. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 176. For example, the polynucleotide may comprise SEQ ID NO: 175. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 204. For example the polynucleotide may comprise SEQ ID NO: 172 or 203. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 230. For example the polynucleotide may comprise SEQ ID NO: 192 or 229.

[0034] In some preferred embodiments, the antibody and antigen-binding fragment light chain CDR1, CDR2, and CDR3 are encoded by polynucleotides comprising SEQ ID NOs: 50, 51, and 52; SEQ ID NOs: 98, 99, and 100; SEQ ID NOs: 74, 75, and 76; SEQ ID NOs: 259, 261, and 263; SEQ ID NOs: 180, 182, and 184; SEQ ID NOs: 152, 154, and 156; or SEQ ID NOs: 208, 210, and 212, respectively. In some preferred embodiments, the antibody and

antigen-binding fragment light chain variable domain is encoded by a polynucleotide comprising SEQ ID NO: 150, 157, 171, 173, 178, 199, or 227.

[0035] In some preferred embodiments, the polynucleotides of the invention encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 158. For example, the polynucleotides may comprise SEQ ID NO: 150 or 157. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 174. For example, the polynucleotide may comprise SEQ ID NO: 173. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 200. For example, the polynucleotide may comprise SEQ ID NO: 171 or 199. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 228. For example the polynucleotide may comprise SEQ ID NO: 178 or 227. In some preferred embodiments, the antibody and antigen-binding fragment light chain sequence is encoded by a polynucleotide comprising SEQ ID NO: 27, 31, 35, 133, 149, 161, 177, 185, 189, 205, 213, 217, or 248.

[0036] In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 68, 69, and 70; and 56, 57, and 58, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 62, 63, and 64; and 50, 51, and 52. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 130, 131, and 132; and 104, 105, and 106, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 123 or 194, 124 or 196, and 125 or 198; and 98 or 180, 99 or 182, and 100 or 184. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 92, 93, and 94; and 80, 81, and 82, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 86 or 166, 87 or 168, and 88 or 170; and 74 or 152, 75 or 154, and 76 or 156. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 144, 146, and 148; and 136, 138, and 140, respectively. For example, the polynucleotide may comprise SEQ ID NOs: 253 or 222, 255 or 224, and 257 or 226; and 259 or 208, 261 or 210, and 263 or 212.

[0037] In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable

domain of SEQ ID NOs: 176 and 174. For example, the polynucleotide may comprise SEQ ID NO: 175 and 173. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 204 and 200. For example, the polynucleotide may comprise SEQ ID NO: 203 or 172 and 199 or 171. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 160 and 158. For example, the polynucleotide may comprise SEQ ID NO: 159 or 164 and 157 or 150. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 230 and 228. For example, the polynucleotide may comprise SEQ ID NO: 229 or 192 and 227 or 178.

[0038] In some preferred embodiments, the polynucleotide encoding the antibodies and antigen-binding fragments can comprise a heavy chain having CDR1 of SEQ ID NO: 62, 86, 123, 166, 194, 222, or 253; CDR2 of SEQ ID NO: 63, 87, 124, 168, 196, 224, or 255; and CDR3 of SEQ ID NO: 64, 88, 125, 170, 198, 212, or 257; and a light chain having CDR1 of SEQ ID NO: 50, 74, 98, 152, 180, 208, or 259; CDR2 of SEQ ID NO: 51, 75, 99, 154, 182, 210, or 261; and CDR3 of SEQ ID NO: 52, 76, 100, 156, 184, 212, or 263. In some preferred embodiments, the polynucleotide encoding the antibodies and antigen-binding fragments can comprise a heavy chain variable domain having SEQ ID NO: 159, 164, 172, 175, 192, 203, or 229 and a light chain variable domain having SEQ ID NO: 150, 157, 171, 173, 178, 199, or 227. In some preferred embodiments, the polynucleotide encoding the antibodies and antigen-binding fragments can comprise a heavy chain sequence of SEQ ID NO: 29, 33, 119, 141, 162, 163, 190, 191, 215, 218, 219, 231, or 250 and a light chain sequence of SEQ ID NO: 27, 31, 35, 133, 149, 161, 177, 185, 189, 205, 213, 217, or 248. Vectors comprising such polynucleotides are also provided.

[0039] The invention also features methods for treating or preventing a Staphylococcus enterotoxin B-mediated disease in a subject in need of such treatment. The methods comprise administering to the subject a composition comprising a pharmaceutically acceptable carrier and at least one antibody that specifically binds to Staphylococcus enterotoxin B in an amount effective to treat or prevent a Staphylococcus enterotoxin B-mediated disease. The invention also features methods for neutralizing Staphylococcus enterotoxin B in subjects in need thereof. The methods comprise administering to the subject at least one inventive antibody that specifically binds to and neutralizes Staphylococcus enterotoxin B in an amount effective to neutralize Staphylococcus enterotoxin B.

[0040] Also featured are methods for making antibodies and antigen-binding fragments that specifically bind to Staphylococcus enterotoxin B. In some embodiments, the methods comprise culturing bone marrow or peripheral blood cells isolated from an animal with the Staphylococcus enterotoxin B or antigenic fragment thereof, isolating B cells that express an antibody that specifically binds to Staphylococcus enterotoxin B, and isolating antibodies produced by said B cells. In some embodiments, the animal is immunized with Staphylococcus enterotoxin B or antigenic fragment thereof prior to isolation of the bone marrow or peripheral blood cells. It is preferable, but not required, that the animal be a mammal, and more preferable, that the animal is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] Figure 1 shows the amino acid sequence of Staphylococcal enterotoxin B (SEB) from *S. aureus* strain ATCC14458 (bold type) (SEQ ID NO: 46). A parallel SEB amino acid sequence is provided (italics) showing differences in the amino acid sequence between SEB and the SEB mutein vaccine (STEB) (dark highlight) (SEQ ID NO: 45) (Boles *et al.* (2003) Clin. Immunol. 108:51-9), and also showing IVIG binding epitopes (single underline) (Nishi *et al.* (1997) J. Immunol. 158:247-54), T-cell receptor-binding H-bonds (double underline) (Li *et al.* (1998) Immunity 9:807-16), and T-cell receptor-binding Van der Waals contacts (light highlight).

[0042] Figure 2 shows an antigen panel ELISA for selection of antigen-specific human mAbs E12, F6, F10, and C5. Antibodies were screened for binding to mucin, goat IgG, BSA, TT, HEL, CAB, BGG, SEB, mesothelin, and GM-CSF. Antibodies with known reactivity against the various antigens were used as positive controls. The murine antibody S5 was used as a positive control to show reactivity with SEB. The E12, F6, F10, and C5antibodies were specific for SEB, and did not cross react with any of the other antigens in the panel. The figure legend identifies the antigens tested and provides the order for the bars on the graph that correspond to the listed antigens.

[0043] Figure 3 shows isotype determination of SEB-specific antibodies E12, F10, F6, and C5. Each antibody was shown to be IgM. E12, F6, and C5 were shown to have a lambda light chain, and F10 was shown to have a kappa light chain.

[0044] Figure 4 shows SEB-dependent proliferation of PBMC with fully human mAbs F6, E12, and C5. The positive control designated as anti-SEB MAb is murine S5. Each antibody induced PBMC proliferation upon neutralization of SEB. Assay medium alone is shown in parallel to demonstrate lack of proliferation.

[0045] Figure 5 shows isotype determination of SEB-specific antibodies 79G9 and 100C9. Both antibodies were shown to be IgG. 79G9 has a kappa light chain, and 100C9 has a lambda light chain.

[0046] Figure 6 shows an antigen panel ELISA for selection of antigen-specific human MAbs 79G9 and 100C9. Antibodies were screened for binding to mucin, goat IgG, BSA, TT, HEL, CAB, BGG, SEB, mesothelin, and GM-CSF. Antibodies with known reactivity against the various antigens were used as positive controls. The murine antibody S5 was used as a positive control to show reactivity with SEB. 79G9 and 100C9 reacted with SEB and the SEB vaccine STEB. No cross-reactivity was observed with the other antigens in the panel. The figure legend identifies the antigens tested and provides the order for the bars on the graph that correspond to the listed antigens.

[0047] Figure 7 shows inhibition of SEB-mediated PBMC mitogenesis by clone 79G9. Increasing concentration of antibody provided increased inhibition of mitogenesis.

[0048] Figure 8 shows dose-dependent inhibition of SEB-mediated PBMC mitogenesis by human monoclonal antibody 79G9.

[0049] Figure 9 shows inhibition of SEB-induced IFN-γ production by antibodies 79G9 and 100C9. When the antibodies were used together, a synergistic or additive effect of inhibition of SEB-induced IFN-γ production was observed. The murine antibody S5 was used as a positive control.

[0050] Figure 10 shows inhibition of SEB induced TNF-α production by antibodies 79G9 and 100C9. When the antibodies were used together, a synergistic or additive effect of inhibition of SEB-induced TNF-α production was observed. The murine antibody S5 was used as a positive control.

[0051] Figure 11 shows an immunoblot demonstrating that human antibodies 79G9 and 100C9 bind to SEB, but not to other human proteins that are present in whole-cell lysate.

[0052] Figure 12 shows that human antibodies 79G9 and 100C9 inhibit IFN-γ and TNF-α production by human T-cells. A synergistic or additive effect is observed when the antibodies are used in tandem.

[0053] Figure 13A-R shows the nucleic acid and amino acid sequences of the H and L chains of antibodies F10 (SEQ ID NOS:27-30, 173-176), 100C9 (SEQ ID NOS:31-34, 157-160, 248-251), 79G9+ (SEQ ID NOS:37-38, 187-188, 201-202), 79G9 (SEQ ID NOS:35-36, 119, 126, 185-186, 199-200, 203-204, 231-232), and 154G12 (SEQ ID NOS:133-134, 141-142, 213-216, 227-230). The bolded regions of the sequences highlight the CDRs, the underlined segment denotes a leader sequence added by PCR, and the shaded regions indicate the variable domain.

[0054] Figure 14A-R shows the CDR and FWR regions of antibodies F10 (SEQ ID NOS:47-70), 100C9 (SEQ ID NOS:71-94), 79G9+ (SEQ ID NOS:107-118), 79G9 (SEQ ID NOS:95-106, 120-125, 127-132), and 154G12 (SEQ ID NOS:135-140, 143-148, 252-263).

[0055] Figure 15 shows the codon optimized nucleic acid sequences of the H and/or L chains of antibodies 100C9 (SEQ ID NO:149-150, 161-164), 79G9 (SEQ ID NOS:171-172, 177, 189-191), and 154G12 (SEQ ID NOS:178, 192, 205, 217-219). The bolded regions of the sequences highlight the CDRs, the underlined segment denotes a leader sequence added by PCR, and the shaded regions indicate the variable domain.

[0056] Figure 16 shows the codon optimized nucleic acid sequences for the CDR and FWR regions of antibodies 100C9 (SEQ ID NOS:151-156, 165-170), 79G9 (SEQ ID NOS:179-184, 193-198), and 154G12 (SEQ ID NOS:207-212, 221-226).

[0057] Figure 17 illustrates sequence differences between 79G9 and 79G9+. Figure 17A shows differences in the nucleotide sequences of 79G9 (SEQ ID NO: 119) and 79G9+ (SEQ ID NO: 37). Figure 17B shows differences in the amino acid sequences of 79G9 (SEQ ID NO: 126) and 79G9+ (SEQ ID NO: 38). Cells producing antibodies comprising the 79G9 heavy chain nucleic acid sequence and 79G9 light chain nucleic acid sequence were deposited with the American Type Culture Collection on January 3, 2007.

[0058] Figure 18 shows binding of antibodies 79G9, 100C9, and 154G12 to Staphylococcus enterotoxins SEA, SED, SEC1, SEC2, and TSST-1; Streptococcal pyrogenic exotoxins SPE-A, SPE-B; and Tetanus toxoid. Hashed bars illustrate binding of control antibodies specific for either TSST-1 or Tetanus toxoid.

DETAILED DESCRIPTION

[0059] For convenience, Table 1 lists each SEQ ID NO and the name of the corresponding sequence.

Table 1. Sequence ID numbers

SEQ ID NO	Sequence Description
1	Primer 390
2	Primer 391
3	Primer 883
4	Primer 974
5	Primer 975
6	Primer 1463
7	Primer 882
8	Primer 885
9	Primer 888

10	Primer 900
11	Primer 1017
12	Primer 1018
13	Primer 1019
14	Primer 1024
15	Primer 1040
16	Primer 1500
17	Primer 1550
18	Primer 1551
19	Primer 1552
20	Primer 1553
21	Leader 2 Nucleotide Sequence
22	Primer 1557
23	Primer 1559
24	Primer 1560
25	Primer 1570
26	Primer 996
27	F10: Light Chain Nucleotide Sequence
28	F10 Light Chain Amino Acid Sequence
29	F10: Heavy Chain Segment Including Variable Domain Nucleotide Sequence
30	F10 Heavy Chain Segment Including Variable Domain Amino Acid Sequence
31	100C9 Light Chain Nucleotide Sequence
32	100C9 Light Chain Amino Acid Sequence
33	100C9 Heavy Chain Nucleotide Sequence
34	100C9 Heavy Chain Amino Acid Sequence
35	79G9 Light Chain Nucleotide Sequence
36	79G9 Light Chain Amino Acid Sequence
37	79G9+ Heavy Chain Nucleotide Sequence
38	79G9+ Heavy Chain Amino Acid Sequence
39	C5 Heavy Chain Variable Domain CDR3 Amino Acid Sequence
40	F6 Heavy Chain Variable Domain CDR3 Amino Acid Sequence
41	C5 Light Chain Variable Domain CDR3 Amino Acid Sequence
42	F6 Light Chain Variable Domain CDR3 Amino Acid Sequence
43	Leader 1 Nucleotide Sequence
44	Leader Amino Acid Sequence
45	STEB
46	SEB
47	F10 Light Chain FWR1 Nucleotide Sequence
48	F10 Light Chain FWR2 Nucleotide Sequence
49	F10 Light Chain FWR3 Nucleotide Sequence
50	F10 Light Chain CDR1 Nucleotide Sequence
51	F10 Light Chain CDR2 Nucleotide Sequence
52	F10 Light Chain CDR3 Nucleotide Sequence
53	F10 Light Chain FWR1 Amino Acid Sequence
54	F10 Light Chain FWR2 Amino Acid Sequence
55	F10 Light Chain FWR3 Amino Acid Sequence
56	F10 Light Chain CDR1 Amino Acid Sequence

57	F10 Light Chain CDR2 Amino Acid Sequence
58	F10 Light Chain CDR3 Amino Acid Sequence
59	F10 Heavy Chain FWR1 Nucleotide Sequence
60	F10 Heavy Chain FWR2 Nucleotide Sequence
61	F10 Heavy Chain FWR3 Nucleotide Sequence
62	F10 Heavy Chain CDR1 Nucleotide Sequence
63	F10 Heavy Chain CDR2 Nucleotide Sequence
64	F10 Heavy Chain CDR3 Nucleotide Sequence
65	F10 Heavy Chain FWR1 Amino Acid Sequence
66	F10 Heavy Chain FWR2 Amino Acid Sequence
67	F10 Heavy Chain FWR3 Amino Acid Sequence
68	F10 Heavy Chain CDR1 Amino Acid Sequence
69	F10 Heavy Chain CDR2 Amino Acid Sequence
70	F10 Heavy Chain CDR3 Amino Acid Sequence
71	100C9 Light Chain FWR1 Nucleotide Sequence
72	100C9 Light Chain FWR2 Nucleotide Sequence
73	100C9 Light Chain FWR3 Nucleotide Sequence
74	100C9 Light Chain CDR1 Nucleotide Sequence
75	100C9 Light Chain CDR2 Nucleotide Sequence
76	100C9 Light Chain CDR3 Nucleotide Sequence
77	100C9 Light Chain FWR1 Amino Acid Sequence
78	100C9 Light Chain FWR2 Amino Acid Sequence
79	100C9 Light Chain FWR3 Amino Acid Sequence
80	100C9 Light Chain CDR1 Amino Acid Sequence
81	100C9 Light Chain CDR2 Amino Acid Sequence
82	100C9 Light Chain CDR3 Amino Acid Sequence
83	100C9 Heavy Chain FWR1 Nucleotide Sequence
84	100C9 Heavy Chain FWR2 Nucleotide Sequence
85	100C9 Heavy Chain FWR3 Nucleotide Sequence
86	100C9 Heavy Chain CDR1 Nucleotide Sequence
87	100C9 Heavy Chain CDR2 Nucleotide Sequence
88	100C9 Heavy Chain CDR3 Nucleotide Sequence
89	100C9 Heavy Chain FWR1 Amino Acid Sequence
90	100C9 Heavy Chain FWR2 Amino Acid Sequence
91	100C9 Heavy Chain FWR3 Amino Acid Sequence
92	100C9 Heavy Chain CDR1 Amino Acid Sequence
93	100C9 Heavy Chain CDR2 Amino Acid Sequence
94	100C9 Heavy Chain CDR3 Amino Acid Sequence
95	79G9 Light Chain FWR1 Nucleotide Sequence
96	79G9 Light Chain FWR2 Nucleotide Sequence
97	79G9 Light Chain FWR3 Nucleotide Sequence
98	79G9 Light Chain CDR1 Nucleotide Sequence
99	79G9 Light Chain CDR2 Nucleotide Sequence
100	79G9 Light Chain CDR3 Nucleotide Sequence
101	79G9 Light Chain FWR1 Amino Acid Sequence
102	79G9 Light Chain FWR2 Amino Acid Sequence
103	79G9 Light Chain FWR3 Amino Acid Sequence
104	79G9 Light Chain CDR1 Amino Acid Sequence
105	79G9 Light Chain CDR2 Amino Acid Sequence

106	79G9 Light Chain CDR3 Amino Acid Sequence
107	79G9+ Heavy Chain FWR1 Nucleotide Sequence
108	79G9+ Heavy Chain FWR2 Nucleotide Sequence
109	79G9+ Heavy Chain FWR3 Nucleotide Sequence
110	79G9+ Heavy Chain CDR1 Nucleotide Sequence
111	79G9+ Heavy Chain CDR2 Nucleotide Sequence
112	79G9+ Heavy Chain CDR3 Nucleotide Sequence
113	79G9+ Heavy Chain FWR1 Amino Acid Sequence
114	79G9+ Heavy Chain FWR2 Amino Acid Sequence
115	79G9+ Heavy Chain FWR3 Amino Acid Sequence
116	79G9+ Heavy Chain CDR1 Amino Acid Sequence
117	79G9+ Heavy Chain CDR2 Amino Acid Sequence
118	79G9+ Heavy Chain CDR3 Amino Acid Sequence
119	79G9 Heavy Chain Nucleotide Sequence
120	79G9 Heavy Chain FWR1 Nucleotide Sequence
121	79G9 Heavy Chain FWR2 Nucleotide Sequence
122	79G9 Heavy Chain FWR3 Nucleotide Sequence
123	79G9 Heavy Chain CDR1 Nucleotide Sequence
124	79G9 Heavy Chain CDR2 Nucleotide Sequence
125	79G9 Heavy Chain CDR3 Nucleotide Sequence
126	79G9 Heavy Chain Amino Acid Sequence
127	79G9 Heavy Chain FWR1 Amino Acid Sequence
128	79G9 Heavy Chain FWR2 Amino Acid Sequence
129	79G9 Heavy Chain FWR3 Amino Acid Sequence
130	79G9 Heavy Chain CDR1 Amino Acid Sequence
131	79G9 Heavy Chain CDR2 Amino Acid Sequence
132	79G9 Heavy Chain CDR3 Amino Acid Sequence
133	154G12 Light Chain Nucleotide Sequence
134	154G12 Light Chain Amino Acid Sequence
135	154G12 Light Chain FWR1 Amino Acid Sequence
136	154G12 Light Chain CDR1 Amino Acid Sequence
137	154G12 Light Chain FWR2 Amino Acid Sequence
138	154G12 Light Chain CDR2 Amino Acid Sequence
139	154G12 Light Chain FWR3 Amino Acid Sequence
140	154G12 Light Chain CDR3 Amino Acid Sequence
141	154G12 Heavy Chain Nucleotide Sequence
142	154G12 Heavy Chain Amino Acid Sequence
143	154G12 Heavy Chain FWR1 Amino Acid Sequence
144	154G12 Heavy Chain CDR1 Amino Acid Sequence
145	154G12 Heavy Chain FWR2 Amino Acid Sequence
146	154G12 Heavy Chain CDR2 Amino Acid Sequence
147	154G12 Heavy Chain FWR3 Amino Acid Sequence
148	154G12 Heavy Chain CDR3 Amino Acid Sequence
149	100C9 Codon Optimized Light Chain Nucleotide Sequence
150	100C9 Codon Optimized Light Chain Variable Domain Nucleotide Sequence
151	100C9 Codon Optimized Light Chain FWR1 Nucleotide Sequence
152	100C9 Codon Optimized Light Chain CDR1 Nucleotide Sequence
153	100C9 Codon Optimized Light Chain FWR2 Nucleotide Sequence

154	100C9 Codon Optimized Light Chain CDR2 Nucleotide Sequence
155	100C9 Codon Optimized Light Chain FWR3 Nucleotide Sequence
156	100C9 Codon Optimized Light Chain CDR3 Nucleotide Sequence
157	100C9 Light Chain Variable Domain Nucleotide Sequence
158	100C9 Light Chain Variable Domain Amino Acid Sequence
159	100C9 Heavy Chain Variable Domain Nucleotide Sequence
160	100C9 Heavy Chain Variable Domain Amino Acid Sequence
161	100C9 Codon Optimized Light Chain Nucleotide Sequence (Minus Leader Sequence)
162	100C9 Codon Optimized Heavy Chain Nucleotide Sequence (Minus Leader Sequence)
163	100C9 Codon Optimized Heavy Chain Nucleotide Sequence
164	100C9 Codon Optimized Heavy Chain Variable Domain Nucleotide Sequence
165	100C9 Codon Optimized Heavy Chain FWR1 Nucleotide Sequence
166	100C9 Codon Optimized Heavy Chain CDR1 Nucleotide Sequence
167	100C9 Codon Optimized Heavy Chain FWR2 Nucleotide Sequence
168	100C9 Codon Optimized Heavy Chain CDR2 Nucleotide Sequence
169	100C9 Codon Optimized Heavy Chain FWR3 Nucleotide Sequence
170	100C9 Codon Optimized Heavy Chain CDR3 Nucleotide Sequence
171	79G9 Codon Optimized Light Chain Variable Domain Nucleotide Sequence
172	79G9 Codon Optimized Heavy Chain Variable Domain Nucleotide Sequence
173	F10: Light Chain Variable Domain Nucleotide Sequence
174	F10 Light Chain Variable Domain Amino Acid Sequence
175	F10: Heavy Chain Variable Domain Nucleotide Sequence
176	F10 Heavy Chain Variable Domain Amino Acid Sequence
177	79G9 Codon Optimized Light Chain Nucleotide Sequence
178	154G12 Codon Optimized Light Chain Variable Domain Nucleotide Sequence
179	79G9 Codon Optimized Light Chain FWR1 Nucleotide Sequence
180	79G9 Codon Optimized Light Chain CDR1 Nucleotide Sequence
181	79G9 Codon Optimized Light Chain FWR2 Nucleotide Sequence
182	79G9 Codon Optimized Light Chain CDR2 Nucleotide Sequence
183	79G9 Codon Optimized Light Chain FWR3 Nucleotide Sequence
184	79G9 Codon Optimized Light Chain CDR3 Nucleotide Sequence
185	79G9 Light Chain Nucleotide Sequence (Minus Leader Sequence)
186	79G9 Light Chain Amino Acid Sequence (Minus Leader Sequence)
187	79G9+ Heavy Chain Nucleotide Sequence (Minus Leader Sequence)
188	79G9+ Heavy Chain Amino Acid Sequence (Minus Leader Sequence)
189	79G9 Codon Optimized Light Chain Nucleotide Sequence (Minus Leader Sequence)
190	79G9 Codon Optimized Heavy Chain Nucleotide Sequence (Minus Leader Sequence)
191	79G9 Codon Optimized Heavy Chain Nucleotide Sequence
192	154G12 Codon Optimized Heavy Chain Variable Domain Nucleotide Sequence
193	79G9 Codon Optimized Heavy Chain FWR1 Nucleotide Sequence
194	79G9 Codon Optimized Heavy Chain CDR1 Nucleotide Sequence

195	79G9 Codon Optimized Heavy Chain FWR2 Nucleotide Sequence
196	79G9 Codon Optimized Heavy Chain CDR2 Nucleotide Sequence
197	79G9 Codon Optimized Heavy Chain FWR3 Nucleotide Sequence
198	79G9 Codon Optimized Heavy Chain CDR3 Nucleotide Sequence
199	79G9 Light Chain Variable Domain Nucleotide Sequence
200	79G9 Light Chain Variable Domain Amino Acid Sequence
201	79G9+ Heavy Chain Variable Domain Nucleotide Sequence
202	79G9+ Heavy Chain Variable Domain Amino Acid Sequence
203	79G9 Heavy Chain Variable Domain Nucleotide Sequence
204	79G9 Heavy Chain Variable Domain Amino Acid Sequence
205	154G12 Codon Optimized Light Chain Nucleotide Sequence
206	Leader 3 Nucleotide Sequence
207	154G12 Codon Optimized Light Chain FWR1 Nucleotide Sequence
208	154G12 Codon Optimized Light Chain CDR1 Nucleotide Sequence
209	154G12 Codon Optimized Light Chain FWR2 Nucleotide Sequence
210	154G12 Codon Optimized Light Chain CDR2 Nucleotide Sequence
211	154G12 Codon Optimized Light Chain FWR3 Nucleotide Sequence
212	154G12 Codon Optimized Light Chain CDR3 Nucleotide Sequence
213	154G12 Light Chain Nucleotide Sequence (Minus Leader Sequence)
214	154G12 Light Chain Amino Acid Sequence (Minus Leader Sequence)
215	154G12 Heavy Chain Nucleotide Sequence (Minus Leader Sequence)
216	154G12 Heavy Chain Amino Acid Sequence (Minus Leader Sequence)
217	154G12 Codon Optimized Light Chain Nucleotide Sequence (Minus Leader Sequence)
218	154G12 Codon Optimized Heavy Chain Nucleotide Sequence (Minus Leader Sequence)
219	154G12 Codon Optimized Heavy Chain Nucleotide Sequence
220	Leader 4 Nucleotide Sequence
221	154G12 Codon Optimized Heavy Chain FWR1 Nucleotide Sequence
222	154G12 Codon Optimized Heavy Chain CDR1 Nucleotide Sequence
223	154G12 Codon Optimized Heavy Chain FWR2 Nucleotide Sequence
224	154G12 Codon Optimized Heavy Chain CDR2 Nucleotide Sequence
225	154G12 Codon Optimized Heavy Chain FWR3 Nucleotide Sequence
226	154G12 Codon Optimized Heavy Chain CDR3 Nucleotide Sequence
227	154G12 Light Chain Variable Domain Nucleotide Sequence
228	154G12 Light Chain Variable Domain Amino Acid Sequence
229	154G12 Heavy Chain Variable Domain Nucleotide Sequence
230	154G12 Heavy Chain Variable Domain Amino Acid Sequence
231	79G9 Heavy Chain Nucleotide Sequence (Minus Leader Sequence)
232	79G9 Heavy Chain Amino Acid Sequence (Minus Leader Sequence)
233	Primer 1015
234	Primer 1020
235	Primer 1321
236	Primer 1461
237	Primer 1530
238	Primer 1578
239	Primer 1582
240	Primer 1730
241	Primer 1731

242	Primer 1732
243	Primer 1733
244	Primer 1734
245	Primer 1735
246	Primer 1736
247	Primer 1737
248	100C9 Light Chain Nucleotide Sequence (Minus Leader Sequence)
249	100C9 Light Chain Amino Acid Sequence (Minus Leader Sequence)
250	100C9 Heavy Chain Nucleotide Sequence (Minus Leader Sequence)
251	100C9 Heavy Chain Amino Acid Sequence (Minus Leader Sequence)
252	154G12 Heavy Chain FWR1 Nucleotide Sequence
253	154G12 Heavy Chain CDR1 Nucleotide Sequence
254	154G12 Heavy Chain FWR2 Nucleotide Sequence
255	154G12 Heavy Chain CDR2 Nucleotide Sequence
256	154G12 Heavy Chain FWR3 Nucleotide Sequence
257	154G12 Heavy Chain CDR3 Nucleotide Sequence
258	154G12 Light Chain FWR1 Nucleotide Sequence
259	154G12 Light Chain CDR1 Nucleotide Sequence
260	154G12 Light Chain FWR2 Nucleotide Sequence
261	154G12 Light Chain CDR2 Nucleotide Sequence
262	154G12 Light Chain FWR3 Nucleotide Sequence
263	154G12 Light Chain CDR3 Nucleotide Sequence
264	Primer 1577
265	Primer 1584

[0060] Various terms relating to the methods and other aspects of the present invention are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0061] The following abbreviations are used throughout the specification. SEB, staphylococcus enterotoxin B; PBMC, peripheral blood mononuclear cells; BSA, bovine serum albumin; TT, tetanus toxoid; HEL, hen egg lysozyme; CAB, chicken albumin; BGG, bovine gamma globulin; TCR, T-cell receptor; CDR, complementarity determining region; FWR, framework region.

[0062] As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a cell" includes a combination of two or more cells, and the like.

[0063] The term "about" as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or ±10%, more preferably ±5%, even more preferably ±1%, and still more preferably ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

[0064] "Isolated" means altered "by the hand of man" from the natural state. If a molecule or composition occurs in nature, it has been "isolated" if it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living plant or animal is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated" as the term is employed herein.

[0065] "Polynucleotide," synonymously referred to as "nucleic acid molecule," refers to any polyribonucleotide or polydeoxyribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. "Polynucleotides" include, without limitation single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short nucleic acid chains, often referred to as oligonucleotides.

[0066] "Substantially the same" with respect to nucleic acid or amino acid sequences, means at least about 65% identity between two or more sequences. Preferably, the term refers to at least about 70% identity between two or more sequences, more preferably at least about 75% identity, more preferably at least about 80% identity, more preferably at least about 85% identity, more preferably at least about 90% identity, more preferably at least about 91% identity, more preferably at least about 92% identity, more preferably at least about 93% identity, more preferably at least about 94% identity, more preferably at least about 95% identity, more preferably at least about 96% identity, more preferably at least about 97% identity, more preferably at least about 98% identity, and more preferably at least about 99% or greater identity.

[0067] A "vector" is a replicon, such as plasmid, phage, cosmid, or virus in which another nucleic acid segment may be operably inserted so as to bring about the replication or expression of the segment.

[0068] The term "operably linked" or "operably inserted" means that the regulatory sequences necessary for expression of the coding sequence are placed in a nucleic acid molecule in the appropriate positions relative to the coding sequence so as to enable expression of the coding sequence. By way of example, a promoter is operably linked with a coding sequence when the promoter is capable of controlling the transcription or expression of that coding sequence. Coding sequences can be operably linked to promoters or regulatory sequences in a sense or antisense orientation. The term "operably linked" is sometimes applied to the arrangement of other transcription control elements (*e.g.*, enhancers) in an expression vector.

[0069] A cell has been "transformed" or "transfected" by exogenous or heterologous nucleic acids such as DNA when such DNA has been introduced inside the cell. The transforming DNA may or may not be integrated (covalently linked) into the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transforming DNA may be maintained on an episomal element such as a plasmid. With respect to eukaryotic cells, a stably transformed cell, or "stable cell" is one in which the transforming DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transforming DNA. A "clone" is a population of cells derived from a single cell or common ancestor by mitosis. A "cell line" is a clone of a primary cell that is capable of stable growth *in vitro* for many generations.

[0070] "Polypeptide" refers to any peptide or protein comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide" refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from natural posttranslational processes or may be made by synthetic methods. Modifications include

acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See, for instance, Proteins - Structure and Molecular Properties, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993 and Wold, F., Posttranslational Protein Modifications: Perspectives and Prospects, pgs. 1-12 in Posttranslational Covalent Modification of Proteins, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, Analysis for Protein Modifications and Nonprotein Cofactors, Meth Enzymol (1990) 182:626-646 and Rattan *et al.*, Protein Synthesis: Posttranslational Modifications and Aging, Ann NY Acad Sci (1992) 663:48-62.

[0071] "Biomolecules" include proteins, polypeptides, nucleic acids, lipids, monosaccharides, polysaccharides, and all fragments, analogs, homologs, conjugates, and derivatives thereof.

[0072] The terms "express" and "produce" are used synonymously herein, and refer to the biosynthesis of a gene product. These terms encompass the transcription of a gene into RNA. These terms also encompass translation of RNA into one or more polypeptides, and further encompass all naturally occurring post-transcriptional and post-translational modifications. The expression/production of an antibody can be within the cytoplasm of the cell, and/or into the extracellular milieu such as the growth medium of a cell culture.

[0073] The terms "treating" or "treatment" refer to any success or indicia of success in the attenuation or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement, remission, diminishing of symptoms or making the injury, pathology, or condition more tolerable to the patient, slowing in the rate of degeneration or decline, making the final point of degeneration less debilitating, improving a subject's physical or mental well-being, or prolonging the length of survival. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neurological examination, and/or psychiatric evaluations.

[0074] "Effective amount" and "therapeutically effective amount" are used interchangeably herein, and refer to an amount of an antibody or composition, as described

herein effective to achieve a particular biological result such as, but not limited to, biological results disclosed, described, or exemplified herein. Such results may include, but are not limited to, the treatment of disease mediated by exposure to Staphylococcus enterotoxin B, as determined by any means suitable in the art.

[0075] "Pharmaceutically acceptable" refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability. "Pharmaceutically acceptable carrier" refers to a medium that does not interfere with the effectiveness of the biological activity of the active ingredient(s) and is not toxic to the host to which it is administered.

[0076] As used herein, the term "inhibition of mitogenesis *in vitro*" means a decrease in the number of cells, in culture, by about 5%, preferably about 10%, more preferably about 20%, more preferably about 30%, more preferably about 40%, more preferably about 50%, more preferably about 60%, more preferably about 70%, more preferably about 80%, more preferably about 90%, and most preferably about 100%. *In vitro* inhibition of mitogenic cell growth may be measured by assays known in the art.

[0077] It is to be understood that this invention is not limited to particular methods, reagents, compounds, compositions or biological systems, which can, of course, 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.

[0078] Staphylococcus toxins are a major virulence factor for infections with *Staphylococcus* bacteria. Exposure to such toxins, whether by ingestion of contaminated food or water, or by inhalation, for example, by means of a terrorist attack, can produce rapid-onset debilitating illness. To date, effective treatments for exposure to Staphylococcus toxins have been slow in coming. It has been discovered in accordance with the present invention that toxins such as Staphylococcus enterotoxin B can be neutralized with antibodies.

[0079] Accordingly, in one aspect, the invention features isolated antibodies and antigen-binding fragments thereof that specifically bind to Staphylococcus enterotoxins, and more specifically, to Staphylococcus enterotoxin B. The antibodies can be polyclonal or monoclonal, or can be derivatives or fragments of antibodies that retain specificity for Staphylococcal enterotoxins. The general structure of an antibody molecule comprises an antigen binding domain, which includes heavy and light chains, and the Fc domain, which serves a variety of functions, including complement fixation.

[0080] There are five classes of immunoglobulins wherein the primary structure of the heavy chain, in the Fc region, determines the immunoglobulin class. Specifically, the alpha, delta, epsilon, gamma, and mu chains correspond to IgA, IgD, IgE, IgG and IgM isotypes, respectively. The inventive antibodies include all isotypes and synthetic multimers of the four-chain immunoglobulin structure. The inventive antibodies also include the IgY isotype generally found in hen or turkey serum and hen or turkey egg yolk. Antibodies non-covalently, specifically, and reversibly bind an antigen.

[0081] Antigen-binding fragments comprise portions of intact antibodies that retain antigen-binding specificity of the parent antibody molecule. For example, antigen-binding fragments can comprise at least one variable region (either a heavy chain or light chain variable region). Examples of suitable antigen-binding fragments include, without limitation antibodies with polyepitopic specificity, bispecific antibodies, diabodies, and single-chain molecules, as well as Fab, F(ab')2, Fd, Fabc, and Fv molecules, single chain (Sc) antibodies, individual antibody light chains, individual antibody heavy chains, chimeric fusions between antibody chains and other molecules, heavy chain monomers or dimers, light chain monomers or dimers, dimers consisting of one heavy and one light chain, and the like. All antibody isotypes can be used to produce antigen-binding fragments. Antigen-binding fragments can be recombinantly produced.

[0082] The antibodies and antigen-binding fragments of the invention can be derived from any species. For example, the antibodies and antigen-binding fragments can be mouse, rat, goat, horse, swine, bovine, chicken, rabbit, donkey, human, and the like. For use in the treatment of humans, non-human derived antibodies and antigen-binding fragments can be structurally altered to be less antigenic upon administration to a human patient.

[0083] In some embodiments of the invention, the antibodies are chimeric antibodies. Chimeric antibodies and methods to produce them are well known and established in the art. As used herein, the term "chimeric antibody" means an antibody, or antigen-binding fragment thereof, having at least some portion of at least one variable domain derived from the antibody amino acid sequence of a non-human mammal, a rodent, or a reptile, while the remaining portions of the antibody, or antigen-binding fragment thereof, are derived from a human. For example, a chimeric antibody may comprise a mouse antigen binding domain with a human Fc or other such structural domain.

[0084] In some embodiments, the antibodies are humanized antibodies. Humanized antibodies can be chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) that contain

minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FWR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies can comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FWR regions are those of a human immunoglobulin sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.* (1986) Nature 321:522-5; Reichmann *et al.* (1988) Nature 332:323-9; and, Presta (1992) Curr. Op. Struct. Biol. 2:593-6.

[0085] In preferred aspects of the invention, the antibodies are fully human. As used herein, the term "human antibody" means that the antibody is either solely from human origin or any antibody in which the variable and constant domain sequences are human sequences. The term encompasses antibodies with sequences derived from (i.e., that utilize) human genes, but which have been changed, e.g., to decrease possible immunogenicity, increase affinity, eliminate cysteines that may cause undesirable folding, etc. The term encompasses such antibodies produced recombinantly in non-human cells, which may impart glycosylation not typical of human cells.

[0086] The antibodies of the invention can be labeled or otherwise conjugated to various chemical or biomolecule moieties, for example, for therapeutic or diagnostic applications. The moieties can be cytotoxic, for example, bacterial toxins, viral toxins, radioisotopes, and the like. The moieties can be detectable labels, for example, fluorescent labels, radiolabels, biotin, and the like.

[0087] Those of skill in the art will recognize that antibody specificity is primarily determined by the six CDR regions, especially H chain CDR3 (Kala *et al.* (2002) J. Biochem. 132:535-41; Morea *et al.* (1998) J. Mol. Biol. 275:269-94; and, Chothia *et al.* (1987) J. Mol. Biol. 196:901-17). Antibody framework regions, however, can play a role in antigen-antibody interactions (Panka *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:3080-4), particularly with respect

to their role in conformation of CDR loops (Foote *et al.* (1992) J. Mol. Biol. 224:487-99). Thus, the inventive antibodies can comprise any combination of H or L chain CDR or FWR regions that confer antibody specificity for SEB. Domain shuffling experiments, which are routinely carried out in the art (Jirholt *et al.* (1998) Gene 215:471-6; Söderlind *et al.* (2000) Nature Biotechnology 18:852-6), can be employed to generate antibodies that specifically bind SEB according to the specifications described and exemplified herein. Antibodies generated by such domain shuffling experiments are within the scope of the present invention.

[0088] Accordingly, in some embodiments, the antibodies comprise a heavy chain CDR1 amino acid sequence substantially the same as or identical to SEQ ID NO: 68, 92, 116, 130, or 144. In some embodiments, the antibodies comprise a heavy chain CDR2 amino acid sequence substantially the same as or identical to SEQ ID NO: 69, 93, 117, 131, or 146. In some particularly preferred embodiments, the antibodies comprise a heavy chain CDR3 amino acid sequence substantially the same as or identical to SEQ ID NO: 39, 40, 70, 94, 118, 132, or 148. In some embodiments, the antibodies comprise a light chain CDR1 amino acid sequence substantially the same as or identical to SEQ ID NO: 56, 80, 104, or 136. In some embodiments, the antibodies comprise a light chain CDR2 amino acid sequence substantially the same as or identical to SEQ ID NO: 57, 81, 105, or 138. In some embodiments, the antibodies comprise a light chain CDR3 amino acid sequence substantially the same as or identical to SEQ ID NO: 58, 82, 106, or 140. In some embodiments, the antibodies comprise a heavy chain FWR1 amino acid sequence substantially the same as or identical to SEQ ID NO: 65, 89, 113, 127, or 143. In some embodiments, the antibodies comprise a heavy chain FWR2 amino acid sequence substantially the same as or identical to SEQ ID NO: 66, 90, 114, 128, or 145. In some embodiments, the antibodies comprise a heavy chain FWR3 amino acid sequence substantially the same as or identical to SEQ ID NO: 67, 91, 115, 129, or 147. In some embodiments, the antibodies comprise a light chain FWR1 amino acid sequence substantially the same as or identical to SEQ ID NO: 53, 77, 101, or 135. In some embodiments, the antibodies comprise a light chain FWR2 amino acid sequence substantially the same as or identical to SEQ ID NO: 54, 78, 102, or 137. In some embodiments, the antibodies comprise a light chain FWR3 amino acid sequence substantially the same as or identical to SEQ ID NO: 55, 79, 103, or 139. Figures 14 and 16 show examples of nucleic acid sequences that can encode the heavy and light chain CDR1-3 and FWR1-3 described in this paragraph.

[0089] The inventive antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30. This heavy chain can be encoded by the nucleic acid sequence that comprises SEQ ID NO: 29. The inventive antibodies can comprise a heavy chain

that comprises the amino acid sequence of SEQ ID NO: 251. This heavy chain can be encoded by a nucleic acid sequence that comprises SEQ ID NO: 250 or 162. The inventive antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 188. This heavy chain can be encoded by the nucleic acid sequence that comprises SEQ ID NO: 37. The inventive antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 232. This heavy chain can be encoded by a nucleic acid sequence that comprises SEQ ID NO: 231 or 190. The inventive antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 216. This heavy chain can be encoded by a nucleic acid sequence that comprises SEQ ID NO: 215 or 218.

[0090] The invention features isolated human antibodies and antigen-binding fragments that specifically bind to, and preferably neutralize Staphylococcus enterotoxin B. The antibodies and antigen-binding fragments can comprise a heavy chain CDR3 having SEQ ID NO: 39, 40, 70, 94, 118, 132, or 148. The antibodies and antigen-binding fragments can comprise heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 68, 69, and 70; SEQ ID NOs: 116, 117, and 118; SEQ ID NOs: 130, 131, and 132; SEQ ID NOs: 92, 93, and 94; or SEQ ID NOs: 144, 146, and 148. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a heavy chain variable domain of SEQ ID NO: 160, 176, 202, 204, or 230. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a heavy chain having SEQ ID NO: 30, 34, 38, 126, 142, 216, 232, or 251.

[0091] In some preferred embodiments, the antibodies and antigen-binding fragments can comprise light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 56, 57, and 58; SEQ ID NOs: 104, 105, and 106; SEQ ID NOs: 80, 81, and 82; or SEQ ID NOs: 136, 138, and 140. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a light chain variable domain of SEQ ID NO: 158, 174, 200, or 228. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a light chain having SEQ ID NO: 28, 32, 36, 134, 186, 214, or 249.**[0092]** In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a heavy chain having CDR1 of SEQ ID NO: 68, 92, 116, 130, or 144; CDR2 of SEQ ID NO: 69, 93, 117, 131, or 146; and CDR3 of SEQ ID NO: 70, 94, 118, 132, or 148; and a light chain having CDR1 of SEQ ID NO: 56, 80, 104, or 136; CDR2 of SEQ ID NO: 57, 81, 105, or 138; and CDR3 of SEQ ID NO: 58, 82, 106, or 140. In some preferred embodiments, the antibodies and antigen-binding fragments can comprise a heavy chain variable domain having SEQ ID NO: 160, 176, 202, 204, or 230 and a light chain variable domain having SEQ ID NO: 158, 174, 200, 228.

[0093] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 68, CDR2 of SEQ ID NO: 69, and CDR3 of SEQ ID NO: 70 and a light chain having CDR1 of SEQ ID NO: 56, CDR2 of SEQ ID NO: 57, and CDR3 of SEQ ID NO: 58. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 176 and a light chain having a variable domain of SEQ ID NO: 174.In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 30 and a light chain having SEQ ID NO: 28.

[0094] In preferred embodiments, the antibody and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 116, CDR2 of SEQ ID NO: 117, and CDR3 of SEQ ID NO: 118, and a light chain having CDR1 of SEQ ID NO: 104, CDR2 of SEQ ID NO: 105, and CDR3 of SEQ ID NO: 106. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 202 and a light chain having a variable domain of SEQ ID NO: 200. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 188 and a light chain having SEQ ID NO: 186.

[0095] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 130, CDR2 of SEQ ID NO: 131, and CDR3 of SEQ ID NO: 132, and a light chain having CDR1 of SEQ ID NO: 104, CDR2 of SEQ ID NO: 105, and CDR3 of SEQ ID NO: 106. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 204 and a light chain having a variable domain of SEQ ID NO: 200. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 232 and a light chain having SEQ ID NO: 186.

[0096] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 92, CDR2 of SEQ ID NO: 93, and CDR3 of SEQ ID NO: 94, and a light chain having CDR1 of SEQ ID NO: 80, CDR2 of SEQ ID NO: 81, and CDR3 of SEQ ID NO: 82. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 160 and a light chain having a variable domain of SEQ ID NO: 158. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 251 and a light chain having SEQ ID NO: 249.

[0097] In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 144, CDR2 of SEQ ID NO:

146, and CDR3 of SEQ ID NO: 148, and a light chain having CDR1 of SEQ ID NO: 136, CDR2 of SEQ ID NO: 138, and CDR3 of SEQ ID NO: 140. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having a variable domain of SEQ ID NO: 230 and a light chain having a variable domain of SEQ ID NO: 228. In preferred embodiments, the antibodies and antigen-binding fragments of the invention comprise a heavy chain having SEQ ID NO: 216 and a light chain having SEQ ID NO: 214.

[0098] The antibodies and antigen-binding fragments are high affinity antibodies and antigen-binding fragments, and can have an affinity of less than about 1×10^{-8} M, preferably less than about 2×10^{-8} M, and more preferably less than about 3×10^{-8} M. Preferably, the antibodies are monoclonal antibodies, and more preferably, are human monoclonal antibodies. Cells that express such antibodies and antigen-binding fragments, such as hybridoma cells and expression cells, are also provided.

[0099] The inventive antibodies can comprise a light chain that comprises the amino acid sequence of SEQ ID NO: 28. This light chain can be encoded by the nucleic acid sequence that comprises SEQ ID NO: 27. The inventive antibodies can comprise a light chain that comprises the amino acid sequence of SEQ ID NO: 249. This light chain can be encoded by a nucleic acid sequence that comprises SEQ ID NO: 31, 248, 161, or 149. The inventive antibodies can comprise a light chain that comprises the amino acid sequence of SEQ ID NO: 186. This light chain can be encoded by a nucleic acid sequence that comprises SEQ ID NO: 185 or 189. The inventive antibodies can comprise a light chain that comprises the amino acid sequence of SEQ ID NO: 214. This light chain can be encoded by a nucleotide sequence comprising SEQ ID NO: 213 or 217.

[0100] It is to be understood that, because of the natural sequence variation likely to exist among heavy and light chains and the genes encoding them, one skilled in the art would expect to find some level of variation within the amino acid sequences or the genes encoding them, while still maintaining the unique binding properties (*e.g.*, specificity and affinity) of the antibodies of the present invention. Such an expectation is due in part to the degeneracy of the genetic code, as well as to the known evolutionary success of conservative amino acid sequence variations, which do not appreciably alter the nature of the encoded protein. Accordingly, such variants and homologs are considered substantially the same as one another and are included within the scope of the present invention.

[0101] The antibodies of the invention thus include variants having single or multiple amino acid substitutions, deletions, additions, or replacements that retain the biological properties (*e.g.*, binding affinity or immune effector activity) of the antibodies of the invention.

The skilled person can produce variants having single or multiple amino acid substitutions, deletions, additions or replacements. These variants may include, *inter alia*: (a) variants in which one or more amino acid residues are substituted with conservative or nonconservative amino acids, (b) variants in which one or more amino acids are added to or deleted from the polypeptide, (c) variants in which one or more amino acids include a substituent group, and (d) variants in which the polypeptide is fused with another peptide or polypeptide such as a fusion partner, a protein tag or other chemical moiety, that may confer useful properties to the polypeptide, such as, for example, an epitope for an antibody, a polyhistidine sequence, a biotin moiety and the like. Antibodies of the invention may include variants in which amino acid residues from one species are substituted for the corresponding residue in another species, either at the conserved or nonconserved positions. In other embodiments, amino acid residues at nonconserved positions are substituted with conservative or nonconservative residues. The techniques for obtaining these variants, including genetic (suppressions, deletions, mutations, etc.), chemical, and enzymatic techniques, are known to the person having ordinary skill in the art.

[0102] In some preferred embodiments, the antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30 and a light chain that comprises the amino acid sequence of SEQ ID NO: 28. In some preferred embodiments, the antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 251 and a light chain that comprises the amino acid sequence of SEQ ID NO: 249. In some preferred embodiments, the antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 188 and a light chain that comprises the amino acid sequence of SEQ ID NO: 186. In some preferred embodiments, the antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 232 and a light chain that comprises the amino acid sequence of SEQ ID NO: 186. In some preferred embodiments, the antibodies can comprise a heavy chain that comprises the amino acid sequence of SEQ ID NO: 216 and a light chain that comprises the amino acid sequence of SEQ ID NO: 214. Those of skill in the art will recognize, however, that in some cases, the pairing of a given heavy with various light chains, or the pairing of a given light chain with various heavy chains will produce antibodies with the same or better specificity and/or affinity than the native combination. Accordingly, the invention is not limited to the preferred combinations of H and L chain pairs, and the inventive antibodies thus encompass different combinations of H and L chain pairs, including without limitation, the H and L chains described herein, or other H or L chains that would be known to those of skill in the

art, or otherwise experimentally determined to be compatible with the H and L chains described herein in order to obtain specific and high affinity binding to SEB.

[0103] The antibodies of the invention have binding affinities (in M) for target antigen that include a dissociation constant (K_D) of less than 1×10^{-2}. In some embodiments, the K_D is less than 1×10^{-3}. In other embodiments, the K_D is less than 1×10^{-4}. In some embodiments, the K_D is less than 1×10^{-5}. In still other embodiments, the K_D is less than 1×10^{-6}. In other embodiments, the K_D is less than 1×10^{-7}. In other embodiments, the K_D is less than 1×10^{-8}, 2×10^{-8}, or 3×10^{-8}. In other embodiments, the K_D is less than 1×10^{-9}. In other embodiments, the K_D is less than 1×10^{-10}, 2×10^{-10}, or 3×10^{-10}. In still other embodiments, the K_D is less than 1×10^{-11}. In some embodiments, the K_D is less than 1×10^{-12}. In other embodiments, the K_D is less than 1×10^{-13}. In other embodiments, the K_D is less than 1×10^{-14}. In still other embodiments, the K_D is less than 1×10^{-15}.

[0104] The inventive antibodies can be modified, *e.g.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from binding to its epitope. Examples of suitable modifications include, but are not limited to glycosylation, acetylation, pegylation, phosphorylation, amidation, and the like. The antibodies of the invention may themselves be derivatized by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other proteins, and the like. The antibodies of the invention may have post-translational moieties that improve upon antibody activity or stability. These moieties include sulfur, methyl, carbohydrate, phosphorus as well as other chemical groups commonly found on immunoglobulin molecules. Furthermore, the antibodies of the invention may contain one or more non-classical amino acids.

[0105] Nucleotide sequences that encode antibodies of the invention are provided. Nucleic acids of the invention include but are not limited to genomic DNA, DNA, cDNA, RNA, double- and single-stranded nucleic acids, and complementary sequences thereof.

[0106] Preferred polynucleotides of the invention include nucleic acid sequences encoding the heavy chain amino acid sequence of SEQ ID NO: 30, 34, 38, 126, 142, 216, 232, or 251. The nucleic acid sequences encoding the light chain amino acid sequence of SEQ ID NO: 28, 32, 36, 134, 186, 214, or 249. Other preferred polynucleotides of the invention include nucleic acid sequences encoding the heavy chain variable domain amino acid sequence of SEQ ID NO: 160, 176, 202, 204, or 230. The nucleic acid sequences encoding the light chain variable domain amino acid sequence of SEQ ID NO: 158, 174, 200, or 228. Other preferred polynucleotides include nucleic acid sequences encoding the antibody CDR3 domains of SEQ ID NOs: 39, 40, 41, 42, 58, 70, 82, 94, 106, 118, 132, 140, or 148; CDR2 domains of SEQ ID NO:

57, 69, 81, 93, 105, 117, 131, 138, or 146. and CDR1 domains of SEQ ID NO: 56, 68, 80, 92, 104, 116, 130, 136, and 144.

[0107] Some preferred examples of polynucleotides encoding the amino acid sequences of the invention include heavy chain polynucleotides of SEQ ID NOs: 29, 33, 37, 119, 141, 162, 163, 190, 191, 215, 218, 219, 231, and 250.; and light chain polynucleotides of SEQ ID NOs: 27, 31, 35, 133, 149, 161, 177, 185, 189, 205, 213, 217, and 248. Other preferred examples of polynucleotides encoding the amino acid sequences of the invention include heavy chain variable domains of SEQ ID NOs: 159, 164, 172, 175, 192, 201, 203, and 229; and light chain variable domains of SEQ ID NOs: 150, 157, 171, 173, 178, 199, and 227. Other preferred examples of polynucleotides encoding the amino acid sequences of the invention include heavy chain CDR1 domains of SEQ ID NOs: 62, 86, 110, 123, 166, 194, 222, and 253; CDR2 domains of SEQ ID NO: 63, 87, 111, 124, 168, 196, 224, and 255; and CDR3 domains of SEQ ID NO: 64, 88, 112, 125, 170, 198, 212, and 257; and light chain CDR1 domains of SEQ ID NO: 50, 74, 98, 152, 180, 208, and 259; CDR2 domains of SEQ ID NO: 51, 75, 99, 154, 182, 210, and 261; and CDR3 domains of SEQ ID NO: 52, 76, 100, 156, 184, 212, and 263. While the polynucleotide sequences described here and elsewhere in the specification provide examples of preferred embodiments of the invention, those of skill in the art will recognize that the degenerate nature of the genetic code provides numerous polynucleotides that will encode the antibodies and antibody fragments of the invention. The invention also features polynucleotides that encode antibodies and antigen-binding fragments that specifically bind to Staphylococcus enterotoxin B. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 68, 69, and 70. For example, the polynucleotide may comprise SEQ ID NOs: 62, 63, and 64. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 116, 117, and 118. For example, the polynucleotide may comprise SEQ ID NOs:110, 111, and 112. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 130, 131, and 132. For example, the polynucleotide may comprise SEQ ID NOs: 123 or 194, 124 or 196, and 125 or 198. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 92, 93, and 94. For example, the polynucleotide may comprise SEQ ID NOs: 86 or 166, 87 or 168, and 88 or 170. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment

having heavy chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 144, 146, and 148. For example, the polynucleotide may comprise SEQ ID NOs: 253 or 222, 255 or 224, and 257 or 226.

[0108] In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 56, 57, and 58. For example, the polynucleotide may comprise SEQ ID NOs: 50, 51, and 52. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 104, 105, and 106. For example, the polynucleotide may comprise SEQ ID NOs: 98 or 180, 99 or 182, and 100 or 184. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 80, 81, and 82. For example, the polynucleotide may comprise SEQ ID NOs: 74 or 152, 75 or 154, and 76 or 156. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 136, 138, and 140. For example, the polynucleotide may comprise SEQ ID NOs: 259 or 208, 261 or 210, and 263 or 212.

[0109] In some preferred embodiments, the antibody or antigen-binding fragment heavy chain variable domain is encoded by a polynucleotide comprising SEQ ID NO: 159, 164, 172, 175, 192, 201, 203, or 229. In some preferred embodiments, the heavy chain sequence is encoded by a polynucleotide comprising SEQ ID NO: 29, 33, 37, 119, 141, 162, 163, 190, 191, 215, 218, 219, 231, or 250. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 160. For example, the polynucleotide may comprise SEQ ID NO: 159 or 164. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 176. For example, the polynucleotide may comprise SEQ ID NO: 175. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 202. For example, the polynucleotide may comprise SEQ ID NO: 201. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 204. For example the polynucleotide may comprise SEQ ID NO: 172 or 203. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain variable domain of SEQ ID NO: 230. For example the polynucleotide may comprise SEQ ID NO: 192 or 229.

[0110] In some preferred embodiments, the antibody and antigen-binding fragment light chain CDR1, CDR2, and CDR3 are encoded by polynucleotides comprising SEQ ID NOs: 50, 51, and 52; SEQ ID NOs: 98, 99, and 100; SEQ ID NOs: 74, 75, and 76; SEQ ID NOs: 259,

261, and 263; SEQ ID NOs: 180, 182, and 184; SEQ ID NOs: 152, 154, and 156; or SEQ ID NOs: 208, 210, and 212. In some preferred embodiments, the antibody and antigen-binding fragment light chain variable domain is encoded by a polynucleotide comprising SEQ ID NO: 150, 157, 171, 173, 178, 199, or 227.

[0111] In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 158. For example, the polynucleotide may comprise SEQ ID NO: 150 or 157. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 174. For example, the polynucleotide may comprise SEQ ID NO: 173. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 200. For example, the polynucleotide may comprise SEQ ID NO: 171 or 199. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a light chain variable domain of SEQ ID NO: 228. For example the polynucleotide may comprise SEQ ID NO: 178 or 227. In some preferred embodiments, the antibody and antigen-binding fragment light chain sequence is encoded by a polynucleotide comprising SEQ ID NO: 27, 31, 35, 133, 149, 161, 177, 185, 189, 205, 213, 217, or 248.

[0112] In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 68, 69, and 70; and 56, 57, and 58; respectively. For example, the polynucleotide may comprise SEQ ID NOs: 62, 63, and 64; and 50, 51, and 52; respectively. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 116, 117, and 118; and 104, 105, and 106; respectively. For example, the polynucleotide may comprise SEQ ID NOs: 110, 111, and 112; and 98 or 180, 99 or 182, and 100 or 184; respectively. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 130, 131, and 132; and 104, 105, and 106; respectively. For example, the polynucleotide may comprise SEQ ID NOs: 123 or 194, 124 or 196, and 125 or 198; and 98 or 180, 99 or 182, and 100 or 184; respectively. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 92, 93, and 94; and 80, 81, and 82; respectively. For example, the polynucleotide may comprise SEQ ID NOs: 86 or 166, 87 or 168, and 88 or 170; and 74 or 152, 75 or 154, and 76 or

156; respectively. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having heavy chain CDR1, CDR2, and CDR3; and light chain CDR1, CDR2, and CDR3 of SEQ ID NOs: 144, 146, and 148; and 136, 138, and 140; respectively. For example, the polynucleotide may comprise SEQ ID NOs: 253 or 222, 255 or 224, and 257 or 226; and 259 or 208, 261 or 210, and 263 or 212; respectively.

[0113] In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 176 and 174. For example, the polynucleotide may comprise SEQ ID NO: 175 and 173. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 202 and 200. For example, the polynucleotide may comprise SEQ ID NO: 201 and 199 or 171. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 204 and 200. For example, the polynucleotide may comprise SEQ ID NO: 203 or 172 and 199 or 171. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 160 and 158. For example, the polynucleotide may comprise SEQ ID NO: 159 or 164 and 157 or 150. In some preferred embodiments, the polynucleotides encode an antibody or antigen-binding fragment having a heavy chain variable domain and a light chain variable domain of SEQ ID NOs: 230 and 228. For example, the polynucleotide may comprise SEQ ID NO: 229 or 192 and 227 or 178.

[0114] In some preferred embodiments, the polynucleotide encoding the antibodies and antigen-binding fragments can comprise a heavy chain having CDR1 of SEQ ID NO: 62, 86, 110, 123, 166, 194, 222, or 253; CDR2 of SEQ ID NO: 63, 87, 111, 124, 168, 196, 224, or 255; and CDR3 of SEQ ID NO: 64, 88, 112, 125, 170, 198, 212, or 257; and a light chain having CDR1 of SEQ ID NO: 50, 74, 98, 152, 180, 208, or 259; CDR2 of SEQ ID NO: 51, 75, 99, 154, 182, 210, or 261; and CDR3 of SEQ ID NO: 52, 76, 100, 156, 184, 212, or 263. In some preferred embodiments, the polynucleotide encoding the antibodies and antigen-binding fragments can comprise a heavy chain variable domain having SEQ ID NO: 159, 164, 172, 175, 192, 201, 203, or 229 and a light chain variable domain having SEQ ID NO: 150, 157, 171, 173, 178, 199, or 227. In some preferred embodiments, the polynucleotide encoding the antibodies and antigen-binding fragments can comprise a heavy chain sequence of SEQ ID NO: 29, 33, 37, 119, 141, 162, 163, 190, 191, 215, 218, 219, 231, or 250 and a light chain sequence of SEQ ID

NO: 27, 31, 35, 133, 149, 161, 177, 185, 189, 205, 213, 217, or 248. Vectors comprising such polynucleotides are also provided.

[0115] In some embodiments, polynucleotides of the invention (and the peptides they encode) include a leader sequence. Any leader sequence known in the art may be employed. The leader sequence may include but is not limited to a restriction site and/or a translation start site. In some preferred embodiments, the leader sequence has the nucleic acid sequence ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTACACAGC (SEQ ID NO: 43), ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCACTCC (SEQ ID NO: 206), ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTCCACTCC (SEQ ID NO: 220), or ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTGCACTCC (SEQ ID NO: 21). In some preferred embodiments, the leader sequence encodes the amino acid sequence MGWSCIILFLVATATGVHS (SEQ ID NO: 44).

[0116] Also encompassed within the present invention are vectors comprising the polynucleotides of the invention. The vectors can be expression vectors. Recombinant expression vectors containing a sequence encoding a polypeptide of interest are thus provided. The expression vector may contain one or more additional sequences such as but not limited to regulatory sequences (*e.g.*, promoter, enhancer), a selection marker, and a polyadenylation signal. Vectors for transforming a wide variety of host cells are well known to those of skill in the art. They include, but are not limited to, plasmids, phagemids, cosmids, baculoviruses, bacmids, bacterial artificial chromosomes (BACs), yeast artificial chromosomes (YACs), as well as other bacterial, yeast and viral vectors.

[0117] Recombinant expression vectors of the invention include synthetic, genomic, or cDNA-derived nucleic acid fragments that encode at least one recombinant protein which may be operably linked to suitable regulatory elements. Such regulatory elements may include a transcriptional promoter, sequences encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. Expression vectors, especially mammalian expression vectors, may also include one or more nontranscribed elements such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, other 5' or 3' flanking nontranscribed sequences, 5' or 3' nontranslated sequences (such as necessary ribosome binding sites), a polyadenylation site, splice donor and acceptor

sites, or transcriptional termination sequences. An origin of replication that confers the ability to replicate in a host may also be incorporated.

[0118] The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells may be provided by viral sources. Exemplary vectors can be constructed as described in Okayama and Berg (1983) *Mol. Cell. Biol.* 3:280.

[0119] In some embodiments, the antibody coding sequence is placed under control of a powerful constitutive promoter, such as the promoters for the following genes: hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, beta-actin, human myosin, human hemoglobin, human muscle creatine, and others. In addition, many viral promoters function constitutively in eukaryotic cells and are suitable for use in the present invention. Such viral promoters include without limitation, Cytomegalovirus (CMV) immediate early promoter, the early and late promoters of SV40, the Mouse Mammary Tumor Virus (MMTV) promoter, the long terminal repeats (LTRs) of Maloney leukemia virus, Human Immunodeficiency Virus (HIV), Epstein Barr Virus (EBV), Rous Sarcoma Virus (RSV), and other retroviruses, and the thymidine kinase promoter of Herpes Simplex Virus. Other promoters are known to those of ordinary skill in the art. In one embodiment, the antibody coding sequence is placed under control of an inducible promoter such as the metallothionein promoter, tetracycline-inducible promoter, doxycycline-inducible promoter, promoters that contain one or more interferon-stimulated response elements (ISRE) such as protein kinase R 2',5'-oligoadenylate synthetases, Mx genes, ADAR1, and the like. Other suitable inducible promoters will be known to those of skill in the art.

[0120] Vectors of the invention may contain one or more Internal Ribosome Entry Site(s) (IRES). Inclusion of an IRES sequence into fusion vectors may be beneficial for enhancing expression of some proteins. In some embodiments the vector system will include one or more polyadenylation sites (*e.g.*, SV40), which may be upstream or downstream of any of the aforementioned nucleic acid sequences. Vector components may be contiguously linked, or arranged in a manner that provides optimal spacing for expressing the gene products (*i.e.*, by the introduction of "spacer" nucleotides between the ORFs), or positioned in another way. Regulatory elements, such as the IRES motif, can also be arranged to provide optimal spacing for expression.

[0121] The vectors may comprise selection markers, which are well known in the art. Selection markers include positive and negative selection markers, for example, antibiotic resistance genes (*e.g.*, neomycin resistance gene, a hygromycin resistance gene, a kanamycin resistance gene, a tetracycline resistance gene, a penicillin resistance gene), HSV-TK, HSV-TK

derivatives for ganciclovir selection, or bacterial purine nucleoside phosphorylase gene for 6-methylpurine selection (Gadi *et al.* (2000) *Gene Ther.* 7:1738-1743). A nucleic acid sequence encoding a selection marker or the cloning site may be upstream or downstream of a nucleic acid sequence encoding a polypeptide of interest or cloning site.

[0122] The vectors of the invention can be used to transform various cells with the genes encoding the various antibodies of the invention. For example, the vectors may be used to generate antibody-producing cells. Thus, another aspect of the invention features host cells transformed with vectors comprising a nucleic acid sequence encoding an antibody that specifically binds SEB, such as the antibodies described and exemplified herein.

[0123] Numerous techniques are known in the art for the introduction of foreign genes into cells and may be used to construct the recombinant cells for purposes of carrying out the inventive methods, in accordance with the various embodiments of the invention. The technique used should provide for the stable transfer of the heterologous gene sequence to the host cell, such that the heterologous gene sequence is heritable and expressible by the cell progeny, and so that the necessary development and physiological functions of the recipient cells are not disrupted. Techniques which may be used include but are not limited to chromosome transfer (*e.g.*, cell fusion, chromosome-mediated gene transfer, micro cell-mediated gene transfer), physical methods (*e.g.*, transfection, spheroplast fusion, microinjection, electroporation, liposome carrier), viral vector transfer (*e.g.*, recombinant DNA viruses, recombinant RNA viruses) and the like (described in Cline (1985) *Pharmac. Ther.* 29:69-92). Calcium phosphate precipitation and polyethylene glycol (PEG)-induced fusion of bacterial protoplasts with mammalian cells can also be used to transform cells.

[0124] Cells transfected with expression vectors of the invention can be selected under positive selection conditions and/or screened for recombinant expression of the antibodies. Recombinant-positive cells are expanded and screened for subclones exhibiting a desired phenotype, such as high level expression, enhanced growth properties, and/or the ability to yield proteins with desired biochemical characteristics, for example, due to protein modification and/or altered post-translational modifications. These phenotypes may be due to inherent properties of a given subclone or to mutagenesis. Mutagenesis can be effected through the use of chemicals, UV-wavelength light, radiation, viruses, insertional mutagens, defective DNA repair, or a combination of such methods.

[0125] Cells suitable for use in the invention for the expression of antibodies are preferably eukaryotic cells, more preferably cells of plant, rodent, or human origin, for example but not limited to NSO, CHO, perC.6, Tk-ts13, BHK, HEK293 cells, COS-7, T98G, CV-

1/EBNA, L cells, C127, 3T3, HeLa, NS1, Sp2/0 myeloma cells, and BHK cell lines, among others. Highly preferred cells for expression of antibodies are hybridoma cells. Methods for producing hybridomas are well established in the art.

[0126] Once a cell expressing the desired protein is identified, it can be expanded and selected. Transfected cells may be selected in a number of ways. For example, cells may be selected for expression of the polypeptide of interest. For cells in which the vector also contains an antibiotic resistance gene, the cells may be selected for antibiotic resistance, which positively selects for cells containing the vector. In other embodiments, the cells may be allowed to grow under selective conditions.

[0127] The invention also features compositions comprising at least one inventive antibody and a pharmaceutically acceptable carrier. Such compositions are useful, for example, for administration to patients to treat or prevent SEB-mediated diseases, such as those described and exemplified herein. The compositions can be formulated as any of various preparations that are known and suitable in the art, including those described and exemplified herein.

[0128] In some embodiments, the compositions are aqueous formulations. Aqueous solutions can be prepared by admixing the antibodies in water or suitable physiologic buffer, and optionally adding suitable colorants, flavors, preservatives, stabilizing and thickening agents and the like as desired. Aqueous suspensions can also be made by dispersing the antibodies in water or physiologic buffer with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0129] Also included are liquid formulations and solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. Such liquid forms include solutions, suspensions, syrups, slurries, and emulsions. Liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats or oils); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). These preparations may contain, in addition to the active agent, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. The compositions may be in powder or lyophilized form for constitution with a suitable vehicle such as sterile water, physiological buffer, saline solution, or alcohol, before use.

[0130] The compositions can be formulated for injection into a subject. For injection, the compositions of the invention can be formulated in aqueous solutions such as water or alcohol, or in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or

physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Injection formulations may also be prepared as solid form preparations which are intended to be converted, shortly before use, to liquid form preparations suitable for injection, for example, by constitution with a suitable vehicle, such as sterile water, saline solution, or alcohol, before use.

[0131] The compositions can be formulated in sustained release vehicles or depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Liposomes and emulsions are well-known examples of delivery vehicles suitable for use as carriers for hydrophobic drugs.

[0132] The invention also features methods for treating or preventing diseases mediated by SEB in subjects in need of such treatment or prevention. In some aspects, the methods can comprise identifying a subject in need of treatment or prevention for SEB-mediated disease. In one embodiment, the methods comprise administering to the subject a composition, such as those described and exemplified herein, the composition comprising a pharmaceutically acceptable carrier and at least one antibody that specifically binds to, and preferably neutralizes, Staphylococcus enterotoxin B, in an amount effective to treat or prevent diseases mediated by SEB. In one embodiment, the methods comprise administering to the subject at least one antibody, such as the antibodies described and exemplified herein, that specifically binds to, and preferably neutralizes, Staphylococcus enterotoxin B, in an amount effective to treat or prevent diseases mediated by SEB.

[0133] As those of skill in the art will understand, SEB is a virulence factor for *Staphylococcus* bacteria that can be produced in individuals with *Staphylococcus spp.* infection. Thus, a subject in need of treatment with SEB-neutralizing antibodies can have an infection with *Staphylococcus* bacteria. The infection can be anywhere in or on the body of the subject, and can be at any stage of infection such as incipient, advanced, or chronic infection such as those observed in patients with implanted medical devices. In addition, as described herein, SEB itself can cause various diseases in patients. SEB can be present apart from the bacteria that produce it, for example, in contaminated food or beverage, or if dispersed in the form of a biological terrorist attack. Accordingly, a subject in need of treatment with SEB-neutralizing antibodies can be exposed to SEB, and not necessarily in conjunction with the bacteria or other cells that express the toxin.

[0134] SEB mediates a variety of disease states in subjects exposed to the toxin. Non-limiting examples of diseases mediated by SEB that can be effectively treated with the inventive methods and inventive SEB-neutralizing antibodies include fever, myalgia, respiratory distress, dyspnea, pleurisy, headache, nausea, vomiting, anorexia, hepatomegaly, and leukocytosis (see, *e.g.*, Ulrich *et al.* (1997) Medical Aspects of Chemical and Biological Warfare, Sidell, Takafuj, and Franz, Eds., in Textbook of Military Medicine, Brigadier Gen. Russ Zajtchuk, Eds., Published by the Office of the Surgeon General at TMM Publications, Borden Institute, Walter Reed Army Medical Center, Washington, DC). Those of skill in the art will know other diseases and complications mediated by SEB that could be treated according to the inventive methods.

[0135] The subject can be any animal, and preferably is a mammal such as a mouse, rat, hamster, guinea pig, rabbit, cat, dog, monkey, donkey, cow, horse, pig, and the like. Most preferably, the mammal is a human.

[0136] In the inventive methods, the at least one antibody is preferably an antibody of the invention. For example, the at least one antibody can comprise a heavy chain having CDR1 of SEQ ID NO: 68, 92, 116, 130, or 144; CDR2 of SEQ ID NO: 69, 93, 117, 131, or 146; and CDR3 of SEQ ID NO: 70, 94, 118, 132, or 148; and a light chain having CDR1 of SEQ ID NO: 56, 80, 104, or 136; CDR2 of SEQ ID NO: 57, 81, 105, or 138; and CDR3 of SEQ ID NO: 58, 82, 106, or 140. In some preferred embodiments, the at least one antibody can comprise a heavy chain variable domain having SEQ ID NO: 160, 176, 202, 204, or 230 and a light chain variable domain having SEQ ID NO: 158, 174, 200, 228.

[0137] In preferred embodiments, the at least one antibody can comprise a heavy chain having CDR1 of SEQ ID NO: 68, CDR2 of SEQ ID NO: 69, and CDR3 of SEQ ID NO: 70 and a light chain having CDR1 of SEQ ID NO: 56, CDR2 of SEQ ID NO: 57, and CDR3 of SEQ ID NO: 58. In preferred embodiments, the at least one antibody can comprise a heavy chain having a variable domain of SEQ ID NO: 176 and a light chain having a variable domain of SEQ ID NO: 174. In preferred embodiments, the at least one antibody can comprise a heavy chain having SEQ ID NO: 30 and a light chain having SEQ ID NO: 28.

[0138] In preferred embodiments, the antibody and antigen-binding fragments of the invention comprise a heavy chain having CDR1 of SEQ ID NO: 116, CDR2 of SEQ ID NO: 117, and CDR3 of SEQ ID NO: 118, and a light chain having CDR1 of SEQ ID NO: 104, CDR2 of SEQ ID NO: 105, and CDR3 of SEQ ID NO: 106. In preferred embodiments, the at least one antibody can comprise a heavy chain having a variable domain of SEQ ID NO: 202 and a light chain having a variable domain of SEQ ID NO: 200. In preferred embodiments, the at least one

antibody can comprise a heavy chain having SEQ ID NO: 188 and a light chain having SEQ ID NO: 186.

[0139] In preferred embodiments, the at least one antibody can comprise a heavy chain having CDR1 of SEQ ID NO: 130, CDR2 of SEQ ID NO: 131, and CDR3 of SEQ ID NO: 132, and a light chain having CDR1 of SEQ ID NO: 104, CDR2 of SEQ ID NO: 105, and CDR3 of SEQ ID NO: 106. In preferred embodiments, the at least one antibody can comprise a heavy chain having a variable domain of SEQ ID NO: 204 and a light chain having a variable domain of SEQ ID NO: 200. In preferred embodiments, the at least one antibody can comprise a heavy chain having SEQ ID NO: 232 and a light chain having SEQ ID NO: 186.

[0140] In preferred embodiments, the at least one antibody can comprise a heavy chain having CDR1 of SEQ ID NO: 92, CDR2 of SEQ ID NO: 93, and CDR3 of SEQ ID NO: 94, and a light chain having CDR1 of SEQ ID NO: 80, CDR2 of SEQ ID NO: 81, and CDR3 of SEQ ID NO: 82. In preferred embodiments, the at least one antibody can comprise a heavy chain having a variable domain of SEQ ID NO: 160 and a light chain having a variable domain of SEQ ID NO: 158. In preferred embodiments, the at least one antibody can comprise a heavy chain having SEQ ID NO: 251 and a light chain having SEQ ID NO: 249.

[0141] In preferred embodiments, the at least one antibody can comprise a heavy chain having CDR1 of SEQ ID NO: 144, CDR2 of SEQ ID NO: 146, and CDR3 of SEQ ID NO: 148, and a light chain having CDR1 of SEQ ID NO: 136, CDR2 of SEQ ID NO: 138, and CDR3 of SEQ ID NO: 140. In preferred embodiments, the at least one antibody can comprise a heavy chain having a variable domain of SEQ ID NO: 230 and a light chain having a variable domain of SEQ ID NO: 228. In preferred embodiments, the at least one antibody can comprise a heavy chain having SEQ ID NO: 216 and a light chain having SEQ ID NO: 214.

[0142] In highly preferred embodiments, the at least one antibody neutralizes SEB. In some aspects of the method, the at least one antibody preferably has an affinity for Staphylococcus enterotoxin B of less than about 1×10^{-8} M, preferably less than about 3×10^{-8} M, more preferably has an affinity for Staphylococcus enterotoxin B of less than about 1×10^{-9} M, and more preferably has an affinity for Staphylococcus enterotoxin B of less than about 1×10^{-10} M, and preferably less than about 3×10^{-10} M.

[0143] Administration of the compositions can be by infusion or injection (intravenously, intramuscularly, intracutaneously, subcutaneously, intrathecal, intraduodenally, intraperitoneally, and the like). The compositions can also be administered intranasally, vaginally, rectally, orally, or transdermally. Preferably, the compositions are administered orally. Administration can be at the direction of a physician.

[0144] Various alternative pharmaceutical delivery systems may be employed. Non-limiting examples of such systems include liposomes and emulsions. Certain organic solvents such as dimethylsulfoxide also may be employed. Additionally, the compositions may be delivered using a sustained-release system, such as semipermeable matrices of solid polymers containing the therapeutic antibodies. The various sustained-release materials available are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the antibodies over a range of several days to several weeks to several months.

[0145] To treat a subject afflicted with SEB-mediated disease, a therapeutically effective amount of the composition is administered to the subject. A therapeutically effective amount will provide a clinically significant abatement in at least one disease mediated by SEB, which can be, but are not limited to, those described and exemplified herein.

[0146] The effective amount of the composition may be dependent on any number of variables, including without limitation, the species, breed, size, height, weight, age, overall health of the subject, the type of formulation, the mode or manner or administration, or the severity of the disease in the subject caused by SEB. The appropriate effective amount can be routinely determined by those of skill in the art using routine optimization techniques and the skilled and informed judgment of the practitioner and other factors evident to those skilled in the art. Preferably, a therapeutically effective dose of the compounds described herein will provide therapeutic benefit without causing substantial toxicity to the subject.

[0147] Toxicity and therapeutic efficacy of agents or compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Agents or compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in the subject. The dosage of such agents or compositions lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

[0148] For any composition used in the methods of the invention, the therapeutically effective dose can be estimated initially from *in vitro* assays such as cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} as determined in cell culture (*i.e.*, the concentration of the composition which achieves a half-maximal inhibition of the osteoclast formation or

activation). Such information can be used to more accurately determine useful doses in a specified subject such as a human. The treating physician can terminate, interrupt, or adjust administration due to toxicity, or to organ dysfunctions, and can adjust treatment as necessary if the clinical response were not adequate in order to improve the response. The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods.

[0149] In one aspect of the inventive methods, the compositions comprise a concentration of at least one anti-SEB antibody in a range of about 0.01% to about 90% of the dry matter weight of the composition. In some embodiments, the at least one anti-SEB antibody comprises up to about 50% of the dry matter weight of the composition. In some embodiments, the at least one anti-SEB antibody comprises up to about 40% of the dry matter weight of the composition. In some embodiments, the at least one anti-SEB antibody comprises up to about 30% of the dry matter weight of the composition. In some embodiments, the at least one anti-SEB antibody comprises up to about 25% of the dry matter weight of the composition. In some embodiments, the at least one anti-SEB antibody comprises up to about 20% of the dry matter weight of the composition. In some embodiments, the at least one anti-SEB antibody comprises up to about 15% of the dry matter weight of the composition. In some embodiments, the at least one anti-SEB antibody comprises up to about 10% of the dry matter weight of the composition.

[0150] In some embodiments, subjects can be administered at least one anti-SEB antibody in a daily dose range of about 0.01 μg to about 500 mg of antibody per kg of the weight of the subject. The dose administered to the subject can also be measured in terms of total amount of the at least one anti-SEB antibody administered per day. In some embodiments, a subject is administered about 5 to about 5000 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 10 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 100 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 250 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 500 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 750 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 1000 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 1500 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 2000 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about

2500 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 3000 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 3500 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 4000 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 4500 milligrams of at least one anti-SEB per day. In some embodiments, a subject is administered up to about 5000 milligrams of at least one anti-SEB per day.

[0151] Treatment can be initiated with smaller dosages that are less than the optimum dose of the at least one anti-SEB, followed by an increase in dosage over the course of the treatment until the optimum effect under the circumstances is reached. If needed, the total daily dosage may be divided and administered in portions throughout the day.

[0152] For effective treatment of SEB-mediated diseases, one skilled in the art may recommend a dosage schedule and dosage amount adequate for the subject being treated. It may be preferred that dosing occur one to four or more times daily for as long as needed. The dosing may occur less frequently if the compositions are formulated in sustained delivery vehicles. The dosage schedule may also vary depending on the active drug concentration, which may depend on the needs of the subject.

[0153] The compositions of the invention for treating SEB-mediated diseases may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, such therapeutic agents can be pain relievers, fever reducers, stomach antacids, compounds which lessen untoward effects of the compositions, or other known agents that treat SEB-mediated diseases.

[0154] The administration of these additional compounds may be simultaneous with the administration of the at least one anti-SEB antibody, or may be administered in tandem, either before or after the administration of the at least one anti-SEB antibody, as necessary. Any suitable protocol may be devised whereby the various compounds to be included in the combination treatment are administered within minutes, hours, days, or weeks of each other. Repeated administration in a cyclic protocol is also contemplated to be within the scope of the present invention.

[0155] The invention also features methods for making an antibody that specifically binds to Staphylococcus enterotoxin B. In some embodiments, the methods comprise isolating bone marrow or peripheral blood cells from an animal, culturing such cells with the Staphylococcus enterotoxin B or an antigenic fragment thereof, isolating B cells from the culture that express an antibody that specifically binds to Staphylococcus enterotoxin B, and isolating

antibodies produced by the B cells. Optionally, the B cells can be fused with donor cells to form a hybridoma, according to any methods that are known in the art. The animal from which bone marrow cells or peripheral blood cells are isolated can be immunized with Staphylococcus enterotoxin B or antigenic fragment thereof prior to isolation of the bone marrow or peripheral blood cells. Any animal can be used in the methods. Preferably, the animals are mammals, and more preferably are humans. In some embodiments, the Staphylococcus enterotoxin B used to immunize the animal, and/or used in the culture with the isolated bone marrow or peripheral blood cells is STEB. STEB has the following amino acid sequence, with residues that differ from SEB underlined: ESQPDPKPDELHKSSKFTGLMENMKVLYDDNHVSAINVKS IDQFRYFDLIYSIKDTKLGNYDNVRVEFKNKDLADKYKDKYVDVFGANAYY QCAFSKKTNDINSHQTDKRKTCMYGGVTEHNGNQLDKYRSITVRVFEDG KNLLSFDVQTNKKKVTAQELDYLTRHYLVKNKKLYEFNNS PYETGYIKFI ENENSFWYDM MPAPGDKFDQSKYLMMYNDNKMVDSKDVKIEVYLTTKKK (SEQ ID NO: 45). For comparison, SEB has the following amino acid sequence: ESQPDPKPDELHKSSKFTGLMENMKVLYDDNHVSAINVKS IDQFLYFDLIYSIKDTKLGNYDNVRVEFKNKDLADKYKDKYVDVFGANYYY QCYFSKKTNDINSHQTDKRKTCMYGGVTEHNGNQLDKYRSITVRVFEDG KNLLSFDVQTNKKKVTAQELDYLTRHYLVKNKKLYEFNNS PYETGYIKFI ENENSFWYDM MPAPGDKFDQSKYLMMYNDNKMVDSKDVKIEVYLTTKKK (SEQ ID NO: 46).

[0156] In some embodiments, the methods for making an antibody that specifically binds to Staphylococcus enterotoxin B comprise comprising culturing a host cell under conditions suitable to produce the antibody, and recovering the antibody from the cell culture. In some embodiments, the host cell can be any cell transformed with a vector comprising the inventive polynucleotides that encode the inventive antibodies and antigen-binding fragments thereof.

[0157] The following examples are provided to describe the invention in greater detail. They are intended to illustrate, not to limit, the invention.

EXAMPLE 1

Generation of Antigen-Specific Fully Human Hybridoma Cell Lines

[0158] Healthy human donors were pre-screened for serum titers to SEB. SEB-specific ELISA were performed by coating TPP Immunomini ELISA plates with 1 μg/ml STEB (SEB

vaccine) dissolved in bicarbonate coating buffer (pH 9.6) (Sigma) overnight at 4°C. The plates were then washed three times with washing buffer (containing 0.5% tween-20), and then blocked with 1x assay buffer for 2 h at room temperature. The blocked plates were incubated at room temperature for 1 h with serial dilutions of normal human plasma (1:100, 1:300, 1:900, 1;2,700, 1:8,100 and 1:24,300) from different donors as well as positive controls (mouse anti-SEB mAb 15D2-1-1 and rabbit anti-SEB PAb FT1009). After incubation with serum, the plates were washed, and incubated with HRP-labeled goat anti-human IgG (H+L) (1:10,000 diluted), HRP-labeled goat anti-mouse IgG (H+L) (1:10,000 diluted) and HRP-labeled goat anti-rabbit IgG (H+L) (1:10,000 diluted) for 1 h at room temperature with shaking. The plates were then washed, and developed with 100 µl TMB substrate per well, and the reaction was stopped by adding 50 µl stop solution (1M H_2SO_4). Developed plates were read at 450 nm on a microtiter plate reader.

[0159] To obtain SEB-reactive B cells, leukopacks were obtained from SEB-positive donors. PBMCs were purified by Ficoll-Paque (GE Healthcare, Piscataway, NJ) density gradient centrifugation. CD20-positive B cells were isolated from PBMCs by negative selection using the EasySep® Human B Cell Enrichment Kit (StemCell Technologies, Vancouver, BC). The enriched B cells were stimulated and expanded using the CD40 culture system.

[0160] B cells were resuspended to a final concentration of 0.2 x 10^6 cells/ml in IMDM (Gibco) supplemented with 10% heat-inactivated human AB serum (Nabi Pharmaceuticals, FL, USA), 4 mM L-glutamine, 10 µg/ml gentamicin (Gibco), 50 µg/ml transferrin (Sigma Chemical Co., ST. Louis, MO) and 5 µg/ml insulin (Sigma Chemical Co.). Enriched B cells were activated via CD40 using CD40 ligand (CD40L) transfected CHO feeder cells. For the co-culture, CD40L-CHO cells were γ-irradiated (96 Gy) and 0.4 x 10^5 cells were plated in 6-well plates. The feeder cells were allowed to adhere overnight at 37°C. A total of 4 ml (0.8 x 10^6) isolated B cells were co-cultured at 37°C for seven to fourteen days with the γ-irradiated CD40L-CHO in the presence of 100 U/ml recombinant human IL-4 (PeproTech) and 0.55 µM CsA (Sigma Chemical Co.).

[0161] Expanded B cells were fused with a myeloma fusion partner via electro-fusion using the CytoPulse CEEF-50 at a 1:1 B cell:myeloma cell ratio. Clones E12, F10, F6, C5, 79G9, and 100C9 were fused with K6H6/B5 myeloma cells (ATCC) and seeded in flat-bottomed 96-well plates in RPMI 1640 (Invitrogen, Carlsbad, CA) supplemented with 10% heat-inactivated FBS (JRH Biosciences, KS, USA), 2 mM L-glutamine, 0.1 mM non-essential amino acids, 1 mM sodium pyruvate, 55 µM 2-Mercaptoethanol, and 1X HAT (100 µM hypoxanthine, 0.4 µM aminopterin and 16 µM thymidine. Clone 154G12 was fused with CBF7 myeloma cells

(Grunow et al. (1990) Dev. Biol. Stand. 71, 3-7; Niedbla and Stott (1998) Hybridoma 17 (3), 299-304) and seeded in flat-bottomed 96-well plates in IMDM (Gibco) supplemented with 10% heat-inactivated human AB serum (Nabi Pharmaceuticals, FL, USA), 4 mM L-glutamine, 10 μg/ml gentamicin (Gibco), 50 μg/ml transferrin (Sigma Chemical Co., ST. Louis, MO) and 5 μg/ml insulin (Sigma Chemical Co.).

[0162] Following cell fusion, culture medium was replaced weekly and HAT selection continued during the antigen-reactivity screening process. Approximately 90% of seeded wells exhibited viable hybridoma cell growth. Hybridomas were screened by ELISA using an attenuated form of recombinant SEB (STEB). Hybridoma clones with SEB reactivity were tested again by ELISA to confirm reactivity and specificity by demonstrating binding to SEB but not to tetanus toxoid (TT). Clones E12, F10, F6, C5, 79G9, 100C9, and 154G12 were highly reactive with SEB but not with TT. Each clone was then subcloned followed by ELISA screening to confirm retention of SEB specificity.

EXAMPLE 2

Characterization of Antibody Specificity

[0163] To further characterize the anti-SEB antibodies, antigen specificity ELISAs were performed using a panel of antigens: SEB, STEB, BGG, CAB, HEL, TT, BSA, human mesothelin, human GM-CSF, human mucin, goat IgG and mouse IgG.

[0164] Antigen-specific ELISA were performed by coating TPP Immunomini ELISA plates with 1 μg/ml STEB (SEB vaccine), 0.5 μg/ml SEB, 2 μg/ml BGG, 2 μg/ml CAB, 2 μg/ml HEL, 1:500 dilution TT, 1%BSA, 0.2 μg/ml human Mesothelin, 2 μg/ml human mucin, 1 μg/ml human GM-CSF, 2 μg/ml goat IgG, 2 μg/ml mouse IgG dissolved in bicarbonate coating buffer (pH 9.6) (Sigma) overnight at 4°C. The plates were then washed three times with washing buffer (containing 0.5% Tween-20), and then blocked with 1X assay buffer for 2 h at room temperature. The blocked plates were incubated at room temperature for 1 h with hybridoma supernatant as well as positive controls. After incubation, the plates were washed, and incubated with HRP-labeled goat anti-human IgG (H+L) (1:10,000 diluted), HRP-labeled goat anti-mouse IgG (H+L) (1:10,000 diluted) or HRP-labeled goat anti-rabbit IgG (H+L) (1:10,000 diluted) for 1 h at room temperature with shaking. The plates were then washed, and developed with 100 μl TMB substrate per well, and the reaction was stopped by adding 50 μl stop solution (1M H_2SO_4). Developed plates were read at 450 nm on a microtiter plate reader. Figures 2 and 6 provide the results of these experiments.

[0165] Figure 2 shows that antibodies E12, F10, F6, and C5 specifically recognize SEB, and show no cross reactivity with the other antigens in the panel. Positive control antibodies for each of the different antibodies were screened in parallel. The positive control antibodies are as follows: Mouse IgG: Goat anti-mouse IgG (Jackson Immunoresearch, Media, PA); Goat IgG: Donkey anti-goat IgG (Jackson Immunoresearch,); BSA, donor serum (prepared in house); TT, donor serum (prepared in house); HEL, rabbit anti-HEL (Fitzgerald Industries International); CAB, mouse anti-chicken egg albumin (Sigma); BGG, rabbit anti-bovine IgG (AbD Serotec, Oxford, UK); mesothelin (anti-mesothelin, prepared in house); GM-CSF (anti-GM-CSF, prepared in house).

[0166] Figure 6 shows that antibodies 100C9 and 79G9 recognize SEB and the vaccine variant of SEB, STEB. The antibodies demonstrated no cross-reactivity with the other antigens in the panel.

EXAMPLE 3

Characterization of Antibody Isotype

[0167] The isotype of each antibody subclone was determined by a standard ELISA using anti-human IgG, IgG1, IgG2, IgG3, IgM, Lk and Ll. Isotype ELISA were performed by coating TPP Immunomini ELISA plates with 2.5 μg/ml Goat anti-human IgG+M (H+L) (from Jackson Immunoresearch) dissolved in bicarbonate coating buffer (pH 9.6) (Sigma) overnight at 4°C. The plates were then washed three times with washing buffer (containing 0.5% Tween-20), and then blocked with 1X assay buffer for 2 h at room temperature. The blocked plates were incubated at room temperature for 1 h with hybridoma supernatant. After incubation, the plates were washed, and incubated with HRP-labeled goat anti-human IgG Fcγ (1:10,000 diluted, from Jackson Immunoresearch), HRP-labeled goat anti-human IgM 5μ (1:10,000 diluted, from Jackson Immunoresearch), HRP-labeled mouse anti-human light chain κ (1:10,000 diluted, from SouthernBiotech) or HRP-labeled mouse anti-human light chain λ (1:10,000 diluted, from SouthernBiotech) for 1 h at room temperature with shaking. The plates were then washed, and developed with 100 μl TMB substrate per well, and the reaction was stopped by adding 50 μl stop solution (1M H_2SO_4). Developed plates were read at 450 nm on a microtiter plate reader.) The results are presented in Figures 3 and 5.

[0168] Figure 3 shows that antibodies E12, F10, F6, and C5 are IgM antibodies. Antibody F10 has a Kappa light chain, and antibodies E12, F6, and C5 have Lambda light chains. Figure 5 shows that antibodies 79G9 and 100C9 are IgG. Antibody 79G9 has a Kappa light chain, and antibody 100C9 has a Lambda light chain.

EXAMPLE 4

Antibody Inhibition of SEB-Mediated PBMC Proliferation

[0169] Human PBMCs from healthy donors were obtained from leukopacks by Ficoll-Paque density gradient centrifugation. Cells were washed three times in complete RPMI. PBMCs were resuspended to 10^6/ml in RPMI 1640 supplemented with 10% fetal bovine serum, 2 mM L-glutamine and 1% penicillin-streptomycin (all purchased from Gibco). One hundred microliters (10^5 cells) were added to the wells of 96 well, flat-bottomed plates in the presence SEB (Toxin Technology, Inc., Sarasota, FL).

[0170] A dose-response curve for SEB was established to determine the appropriate toxin concentration for the neutralization studies. To evaluate neutralization activity, 100 µl of SEB (50 pg/ml) was incubated for 1 hour at 37°C with culture supernatants from SEB-reactive human B cell hybridomas prior to the addition of PBMCs. Murine anti-SEB monoclonal antibody clone S5 (Fitzgerald Industries International, Inc., Concord, MA) was used as a positive control for the inhibition of SEB mediated stimulation. The cultures were incubated at 37°C for three days, followed by another 24 hours of culture in the presence of 5-bromo-2'-deoxyuridine (BrdU). Cell proliferation was assessed by measuring BrdU incorporation by ELISA (Roche Applied Science, Indianapolis, IN). Percent inhibition was calculated according to the formula 100-[O.D. with anti-SEB Ig/O.D. with SEB only] x 100.

[0171] Figure 4 demonstrates inhibition of SEB mediated PBMC proliferation with fully human mAbs F6, E12, and C5. Murine anti-SEB antibody S5 was screened in parallel as a positive control. The three antibodies were able to significantly inhibit SEB-induced PBMC proliferation at levels comparable to the control antibody.

[0172] Figure 7 demonstrates that antibody 79G9 inhibited SEB-mediated PBMC mitogenesis. Increasing concentrations of 79G9 increased the percent inhibition of the mitogenesis. Figure 8 demonstrates inhibition of SEB mediated PBMC proliferation with antibody 79G9. Increasing concentrations of the antibody increased the level of inhibition of the proliferation.

EXAMPLE 5

Cytokine bioassays

[0173] The ability of the human antibodies to inhibit SEB-induced proinflammatory cytokine production was studied with human PBMCs as follows. A dose-response curve for SEB (Toxin Technology, Inc.) was first determined. Fresh human PBMC were obtained from

healthy adult donors and purified by Ficoll-Paque Plus (Amersham-Pharmacia). Approximately 1×10^5 cells in 200 µl of cIMDM medium supplemented with 10% heat-inactivated fetal bovine serum (Gibco BRL), 2 mM L-glutamine (Gibco BRL) were cultured in 96-well flat-bottom tissue culture plates (Falcon Labware) and incubated with various concentrations of SEB for 18-22 hrs at 37°C in 5% CO_2. Culture supernatants were transferred to IFN-γ and TNF-α coated plates (75 µl/well) and assayed using ELISA kit (R&D System) according to manufacture protocols. SEB EC_{50} values were calculated using graph package Prism4 (GraphPad Software). For neutralization studies, various concentrations of antibodies were preincubated with SEB (at either 4x or 1x EC_{50}) for 1 h at 37°C prior to the addition of cells. The sensitivity limit of the IFN-γ and TNF-α assay were 16 pg/ml.

[0174] Table 2 shows the raw data of IFN-γ inhibition by the antibody, 79G9. 79G9 at 2.5 µg/ml inhibits SEB induced IFN-γ production to below detection. Figure 9 shows the converted data where percentage of inhibition was graphed using graph package Prism4 (GraphPad Software). The data show that either 79G9 or 100C9 alone could block SEB-induced abnormal secretion of IFN-γ, to the same extent, or even more effectively than the positive control anti-SEB mouse antibody S5 (EC_{50} of 0.125 µg/ml and 0.07665 µg/ml vs. 0.2517 µg/ml). In addition, when the two antibodies 79G9 and 100C9 were used in combination, a synergistic or additive effect of SEB neutralization was observed, with the antibodies exhibiting a combined EC_{50} of 0.0188 µg/ml. Figure 10 shows that similar results are obtained in an assay for TNF-α inhibition. As observed for IFN-γ, 79G9 and 100C9 were found to inhibit TNF-α production at or above levels inhibited by S5. Similarly, a synergistic or additive effect for 79G9 and 100C9 was also observed for TNF-α inhibition. Figure 12 shows a graph of calculated EC_{50} values for TNF-α and IFN-γ inhibition. The synergistic or additive effect of 79G9 and 100C9 is shown in the graph.

Table 2. Production of IFN-γ with 79G9 cytokine bioassay.

79G9 Concentration (µg/ml)	IFN-γ (pg/ml)
20	<16
10	<16
5	<16
2.5	<16
1.25	21
0.625	20
0.313	28

0.156	24
0.078	38
0.039	37
No Ab (Cells + SEB)	59

EXAMPLE 6

Analysis of anti-SEB antibodies binding kinetics and antibody competition

[0175] SEB was diluted in sodium acetate buffer, pH 5.0, to a concentration of 5 µg/ml and coupled to a CM5 chip using standard amine chemistry with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) to a level of 10.8 RU bound on a BIAcore® 3000 instrument running BIAcore® 3000 Control software, version 3.2. The remaining active sites were quenched with 1M ethanolamine. A reference flow cell was prepared as a control by activation with EDC and NHS and subsequent quenching with ethanolamine without the administration of SEB ligand. A surface-performance analysis was performed on the chip using 500 nM 100C9 antibody and 10 mM HCl as regeneration solution to confirm stable response and baseline. Mass transport effects were evaluated by analyzing association and dissociation of selected anti-SEB antibodies at flow rates of 10 µl/min, 45 µl/min, and 70 µl/min. Rates varied by less than 10% over the range of flow rates tested, indicating little or no mass transport limitations.

[0176] To analyze antibody binding kinetics, purified anti-SEB monoclonal antibodies were diluted to 1000 nM, 333.3 nM, 111.1 nM, 37.0 nM, 12.3 nM, 4.1 nM, 1.4 nM, 0.46 nM, and 0 nM in HBS-EP buffer (BIAcore®). Samples were randomly injected at a flow rate of 30 µL/min (total injected volume was 250 µL) first over the reference cell then the SEB-coupled cell. Dissociation was observed for 30 minutes. Regeneration of the chip following each cycle was accomplished by two 50 µl injections of 10 mM HCl at a flow rate of 100 µl/min. All subsequent data analysis was performed in BIAevaluation software, version 4.1. Sensograms were first normalized by subtraction of data from blank injections to remove bulk effects and instrument noise. Association (k_{a1}) and dissociation (k_{d1}) rate constants for the binding reaction A + B = AB (where A is anti-SEB analyte and B is SEB ligand) were determined simultaneously by global fit of the data for each antibody analyzed to a bivalent analyte binding model. A steady state binding constant (K_{D1}) for the above interaction was determined by the relationship $K_{D1} = k_{d1}/k_{a1}$ (Table 3).

[0177] **Table 3**. Binding kinetics for anti-SEB antibodies 79G9, 100C9, and 154G12.

Anti-SEB Antibody	k_{a1} ($x10^3$ $M^{-1}sec^{-1}$)	k_{d1} ($x10^{-4}$ sec^{-1})	K_{D1} (nM)
79G9	9.56	2.39	25.00
100C9	159.0	15.5	9.75
154G12	93	0.271	0.29

[0178] To determine whether binding competition occurred, anti-SEB monoclonal antibodies were injected at a concentration of 1 μM onto the ligand-bound chip, as described above. This concentration was chosen because, for all antibodies, this was 10- to 100-fold greater than the K_{D1}. Under these conditions, all, or nearly all, of the available binding sites should be occupied. This was followed by a second injection of the same antibody to confirm equilibrium state had been reached. A third, non-similar antibody was then injected at a concentration of 1 μM . The chip was subsequently regenerated with two 50 μL injections of 10 mM HCl. The degree of binding ($R_{eq'}$) of the second antibody was compared with the level of binding achieved on an unoccupied chip (R_{eq}). The ratio of $R_{eq'}/R_{eq}$ was then calculated; a ratio close to or equal to 1 indicated that the antibodies do not compete and bind independently to SEB, while a ratio of much less than 1 indicated significant overlap in binding sites (Table 4).

[0179] **Table 4**. Binding competition for anti-SEB antibodies 79G9, 100C9, and 154G12.

1st mAb	2nd mAb	R_{eq}	$R_{eq'}$	$R_{eq'}/R_{eq}$
154G12	79G9	19.4	16.8	0.87
154G12	100C9	22.2	0	0.00
79G9	154G12	33	27.3	0.83
79G9	100C9	22	14.9	0.68

[0180] The results shown in Table 4 indicate that 79G9 and 154G12 do not compete , and that they can bind independent of one another and do not have overlapping epitopes. However, these data also indicate that 154G12 and 100C9 do compete highly with one another and thus have overlapping epitopes. 79G9 slightly inhibits subsequent binding of 100C9, and thus these two antibodies may have neighboring epitopes. Due to the rapid dissociation rate of 100C9 and the difficulty of assessing effects on binding of a subsequent antibody, 100C9 was not tested as the first antibody.

EXAMPLE 7

Human Anti-SEB Antibodies Neutralize SEB Activity *in vitro* and *in vivo*

[0181] Human anti-SEB monoclonal antibodies 79G9 and 100C9 are two independent human IgG4 highly specific to SEB that were derived as follows. Human B-cells from healthy donors were immunized *ex vivo* with SEB-derived peptides and fused to a cell partner to derive >2,000 hybridomas. Clones secreting SEB-specific mAbs were identified robotically using an ELISA method employing SEB-coated plates. Lead hybridomas secreting mAbs for which specific binding was confirmed by subsequent analyses were further expanded and characterized. Figure 6 shows that 79G9 and 100C9 specifically bound purified SEB and STEB (the USAMRIID's vaccine candidate) and did not cross-react with other unrelated purified proteins tested. When used for immunoblotting, antibodies only reacted to SEB and showed no crossreactivity to the thousands of proteins present in a human cell lysate (Figure 11). 100C9 binds to SEB more strongly relative to 79G9 as determined by ELISA (data not shown).

[0182] To determine biological activity of 79G9 and 100C9 *in vivo,* Balb/C mice were challenged with SEB and treated with 79G9 alone or in combination with 100C9. Because in this model mice are fairly insensitive to the toxin, lipopolysaccaride (LPS) needs to be injected to boost the animal response to SEB. The SEB challenge corresponded to approximately 10 (Study 1) or 25 (Study 2) 50% lethal dose (LD_{50}), or 2-5 μg of SEB/mouse delivered i.p. Based on the *in vitro* data, it was estimated that a Antibody:SEB molar ratio around 100:1 would be sufficient (molecular weights for antibodies and SEB are approximately 150 and 30 kD, respectively) and therefore antibody dose did not exceed 1 mg/mouse (1,000 μg antibody : 2 μg SEB : 5 [weight difference] = 100). In Study 1 (Table 5), a 79G9:SEB molar ratio of 100:1 protected 100% of the mice (5 of 5 animals) compared to no survivors (0 in 4) in the untreated group. SEB or LPS alone did not cause lethality.

Table 5. Survival of mice exposed to SEB and treated with Anti-SEB antibodies, Study 1.

Balb/C SEB/LPS challenge model					
Group	**SEB LD_{50}**	**Treatment**	**Dose (μg)**	**Survivors/Total Mice**	
				18 Hours	**72 Hours**
1	0 (no LPS)	-	-	2/2	2/2
2	0 (with LPS)	-	-	4/4	4/4
3	10	-	-	2/4	0/4
4	10	79G9	1 mg	5/5	5/5

[0183] SEB exposure was increased to 25 LD_{50} in Study 2 (Table 6). No treatment or control human IgG were unable to rescue mice from SEB toxicity. By contrast, 3 of 5 mice survived the SEB exposure either when mice were treated with 79G9 alone (1 mg) at a 79G9:SEB ratio of 40:1, or when treated with a combination of 79G9 and 100C9 (0.1 mg each) with a combined Antibody:SEB ratio of just 8:1. This combination led to 100% survival (5 of 5 mice) using a Antibody:SEB ratio of 40:1 (0.5 mg of each antibody).

Table 6. Survival of mice exposed to SEB and treated with Anti-SEB antibodies, Study 2.

Balb/C SEB/LPS challenge model					
Group	**SEB LD_{50}**	**Treatment**	**Dose (μg)**	**Survivors/Total Mice**	
				18 Hours	**72 Hours**
1	25	-	-	1/3	0/3
2	25	Control Human IgG	1 mg	1/3	0/3
3	25	79G9	1 mg	5/5	3/5
4	25	79G9 + 100C9	0.1 + 0.1 mg	5/5	3/5
5	25	79G9 + 100C9	0.5 + 0.5 mg	5/5	5/5

EXAMPLE 8

Nucleotide and Amino Acids Sequences Encoding Fully Human Anti-SEB Antibodies F10, 79G9 and 100C9

[0184] Nucleotide and amino acid sequences for fully human anti-SEB antibodies were obtained by standard molecular biology methods. Briefly, total RNA was isolated from hybridomas F10, 79G9, and 100C9 using Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. The message was synthesized to cDNA using Superscript II reverse transcriptase (Invitrogen) according to the manufacturer's instructions.

[0185] To amplify the light and heavy chain variable regions, PCR reactions were carried out with Herculase DNA polymerase (Stratagene, La Jolla, CA). Primers used for the heavy and light chain amplification for each antibody are set forth in Table 7 below.

Table 7. PCR primers for Amplification of Nucleotide Sequences for Antibodies to SEB

Primer	Sequence (5' – 3')	SEQ ID NO:
390	CCCAGTCACGACGTTGTAAAACG	1
391	AGCGGATAACAATTTCACACAGG	2
883	TGGAAGAGGCACGTTCTTTTCTTT	3
974	AGGTRCAGCTGBWGSAGTCDG	4
975	GAHRTYSWGHTGACBCAGTCTCC	5
1463	GATCGAATTCTTAACACTCTCCCCTGTT GAAGCTCTTTGTGACGGGCGAGCTCAGGCC	6
882	GTCCACCTTGGTGTTGCTGGGCTT	7
885	TGAAGATTCTGTAGGGGCCACTGTCTT	8
888	GAGGTGCAGCTGGTGGAGTCTGG	9
900	TCCTATGTGCTGACTCAGCCACC	10
1017	TGCAAGGTCTCCAACAAAGC	11
1018	CCTGGTTCTTGGTCAGCTCA	12
1019	GGCACGGTGGGCATGTGTGA	13
1024	ACCAAGGGCCCATCGGTCTT	14
1040	GCAACACCAAGGTGGACAAG	15
1500	GGTTCAGGGGGAGGTGTGGGAGGT	16
1550	GGGAAGCTTGCCGCCACCATGGGATGGAGCTGT ATCATCCTCTTCTTGGTAGCAACAGCTACAGGTG TACACAGCTCCTATGTGCTGACTCAGCCACC	17
1551	CCCGAATTCCTATGAAGATTCTGTAGGGGCCACTGTCTT	18
1552	GGGAAGCTTGCCGCCACCATGGGATGGAGCTG TATCATCCTCTTCTTGGTAGCAACAGCTACAGG TGTACACAGCGAGGTGCAGCTGGTGGAGTCTGGG	19
1553	CCCGAATTCTCATTTACCCAGAGACAGGGAGAGGCTCTTCTG	20
1557	GGGAAGCTTGCCGCCACCATGGGATGGAGCTGTATCAT CCTCTTCTTGGTAGCAACAGCTACAGGTGTACACAGCG ACATTGAGTTGACCCAGTCTCCA	22
1559	GGGAAGCTTGCCGCCACCATGGGATGGAGCTGTATCAT CCTCTTCTTGGTAGCAACAGCTACAGGTGTACACAGCGT	23

	ACAGCTGTTGGAGTCTGGCGCA	
1560	CCCTTCGAATTAATCACTCTCCCCTGTTGAAGCTCTTTG	24
1570	GGGAAGCTTGCCGCCACCATGGGATGGAGCTGTATCATCCTC TTCTTGGTAGCAACAGCTACAGGTGTACACAGCGAGGTACAG CTGTTGGAGTCTGGCGCA	25
996	GATCGAATTCTCATTTCCCGGGAGACAGGGAGAGG	26
1015	GGTTCGCTTATTGGGGCCAA	233
1020	CGGTGTCTTCGGGTCTCAGG	234
1321	GGAGGGCAGTGTAGTCTGAG	235
1461	CCTCTACAAATGTGGTATGGCTGATTATG	236
1530	GGGAACGGTGCATTGGAACG	237
1577	CCCAAGCTTGCCGCCACCATGGGATGGAGCTGTATCATCCTC TTCTTGGTAGCAACAGCTACAGGTGTCCACTCCSAGGTRCAGC TGBWGSAGTCDG	264
1578	CCCAAGCTTGCCGCCACCATGGGATGGAGCTGTATCATCCTC TTCTTGGTAGCAACAGCTACAGGTGTCCACTCCGAHRTYSWG HTGACBCAGTCTCC	238
1582	CCCGAATTCTCATGAAGATTCTGTAGGGGCCACTGTCTT	239
1584	CCCGAATTCTCATTTACCCGGAGACAGGGAGAGGCTCTTC	265
1730	ACGCCGTCCACGTACCAATT	240
1731	AAGCCCTTCACCAGACAGGT	241
1732	TGGTGGACGTGTCCCACG	242
1733	GGAAGGGCCCTTGGTGGA	243
1734	ACCGTGGCCGCTCCTTCC	244
1735	TGCAGGGCGTTGTCCACC	245
1736	AGGCCGCTCCCTCCGTGA	246
1737	TTCACAGGGGAGGAGTCAG	247

In the above table, R = A or G; B = C or G or T; W = A or T; S = C or G; D = A or G or T; H = A or C or T; Y = C or T.

[0186] PCR products were cloned into pCR4-TOPO vector (Invitrogen), transformed into *E. coli* Mach1 cells and transformants were selected on LB-Kanamycin plates. Colonies were screened for inserts using the same primer pairs used for PCR amplification, and four positive colonies each were used to generate template DNA for DNA sequence determination, using TempliPhi reagent (GE Healthcare).

[0187] DNA inserts were sequenced using primers SEQ ID NO: 1 and 2, with Beckman Coulter DTCS sequencing reagent, followed by data acquisition and analysis on a Beckman Coulter CEQ2000. To add a leader peptide sequence to the light chain, a positive clone was re-amplified with primers SEQ ID NOs:17 and 18 (for 100C9), and SEQ ID NOs 22 and 24 (for 79G9) using Herculase DNA polymerase. To generate a full length heavy chain including a leader peptide sequence, PCR was carried out with primers SEQ ID NOs 19 and 20 (for 100C9), and SEQ ID NOs: 25 and 26 (for 79G9) using the original cDNA as template. The resulting PCR product was TA cloned, transformed into Mach1 cells and positive clones were identified as described above.

[0188] Full length heavy chain cDNA was sequenced using primers SEQ ID NOs: 1, 2, 11, 12, 13, 14, 15, 16, 19, and 20 (for 100C9), and SEQ ID NOs: 1, 2, 11, 12, 13, 14, and 15 (for 79G9) using template DNA generated with TempliPhi reagent. The resulting DNA sequences for the full length heavy chain variable regions are as follows: F10 (SEQ ID NO: 29); 100C9 (SEQ ID NO: 250); 79G9+ (SEQ ID NO: 201); 79G9 (SEQ ID NO: 231). It should be pointed out that the heavy chain nucleic acid sequence for 79G9 represents a corrected nucleic acid sequence for 79G9+ (Figure 17). The resulting DNA sequences for the full length light chain variable regions are follows: F10 (SEQ ID NO: 173); 100C9 (SEQ ID NO: 248); 79G9 (SEQ ID NO: 185). The predicted amino acid sequences derived from the heavy chain nucleic acid sequences are as follows: F10 (SEQ ID NO: 30); 100C9 (SEQ ID NO: 251); 79G9+ (SEQ ID NO: 188); 79G9 (SEQ ID NO: 232). The predicted amino acid sequences derived from the light chain nucleic acid sequences are as follows: F10 (SEQ ID NO: 28); 100C9 (SEQ ID NO: 249); 79G9 (SEQ ID NO: 186).

[0189] The nucleic acid and amino acid sequences for each of these antibodies is presented in Figure 13 A-N. The underlined portions of the sequence represent the leader sequence added by PCR. The bolded regions of the sequences highlight the CDRs. The shaded regions indicate the variable domain. Figure 14 A-N provides the sequences for CDR and FWR regions for antibodies F10, 100C9, and 79G9.

[0190] The VH and VL CDR3 region sequences were additionally obtained for hybridomas C5 and F6. Total RNA was isolated from hybridomas C5 and F6 using Trizol reagent (Invitrogen) according to the manufacturer's instructions. cDNA was synthesized using Superscript II reverse transcriptase (Invitrogen) according to the manufacturer's instructions. To amplify the light and heavy chain variable regions, PCR reactions were carried out with Herculase DNA polymerase (Stratagene) using Morphotek primers # 885 (SEQ ID NO: 8) and # 900 (SEQ ID NO: 10) for the light chains and #974 (SEQ ID NO: 4) and #883 (SEQ ID NO: 3)

for the heavy chains. PCR products were cloned into pCR4-TOPO vector (Invitrogen), transformed into *E. coli* Mach1 cells and transformants were selected on LB Kanamycin plates. Colonies were screened for inserts with the same primer pairs as above and 4 positive colonies each were used to generate template DNA for DNA sequence determination, using TempliPhi reagent (GE Healthcare). DNA inserts were sequenced with Morphotek primers # 390 (SEQ ID NO: 1) and #391 (SEQ ID NO: 2) using Beckman Coulter DTCS sequencing reagent followed by data acquisition and analysis on a Beckman Coulter CEQ2000. The predicted CDR3 translated amino acid sequences are shown below in Table 8.

Table 8. Variable region sequences for IgM hybridoma subclones C5, and F6.

Hybridoma	**VH CDR3 Sequence**	**Closest Germline Match (VH)**	**SEQ ID NO:**
C5	CSAAGTVDYWGQG	VH3-30	39
F6	CTTMRNWGQG	VH3-15	40
Hybridoma	**VL CDR3 Sequence**	**Closest Germline Match (VL)**	**SEQ ID NO:**
C5	CQSADSSGTYVFGTG	V2-17	41
F6	CQSADSSGTYVVFGGG	V2-17	42

EXAMPLE 9

Cloning and sequencing of human IgG anti-SEB antibody 154G12

[0191] Nucleotide and amino acid sequences for human IgG anti-SEB antibody 154G12 was obtained by standard molecular biology methods. Total RNA was isolated from hybridoma 154G12 using Trizol® reagent (Invitrogen) according to the manufacturer's instructions. Superscript II reverse transcriptase (Invitrogen) was used to synthesize 154G12 cDNA from the isolated total RNA according to the manufacturer's instructions.

[0192] To amplify the light and heavy chain nucleic acid sequences, PCR was carried out with Herculase® DNA polymerase (Stratagene) using primers #1578 (SEQ ID NO: 238) and #1582 (SEQ ID NO: 239) for the light chain, and #1584 (SEQ ID NO: 265) and #1577 (SEQ ID NO: 264) for the heavy chain (Table 7). The 5' primers for both chain amplifications contain leader peptides for eukaryotic expression.

[0193] The resulting PCR products were cloned into pCR4-TOPO vector (Invitrogen), transformed into *E. coli* Mach1 cells, plated on LB Kanamycin agar plates, and selected for

Kanamycin resistance. Colonies were screened for inserts using primers #1578 (SEQ ID NO: 238) and #1582 (SEQ ID NO: 239) for the light chain, and #1584 (SEQ ID NO: 265) and #1577 (SEQ ID NO: 264) for the heavy chain (Table 7). Four positive colonies each were used to generate template DNA for DNA sequence determination, using TempliPhi reagent (GE Healthcare).

[0194] Light chain DNA inserts were sequenced with primers #1321 (SEQ ID NO: 235), 1461 (SEQ ID NO: 236), 1500 (SEQ ID NO: 16), 1551 (SEQ ID NO: 18), and 1552 (SEQ ID NO: 19) (Table 7) using Beckman Coulter DTCS sequencing reagent followed by data acquisition and analysis on a Beckman Coulter CEQ2000. Full length 154G12 heavy chain cDNA was sequenced with primers #996 (SEQ ID NO: 26), 1015 (SEQ ID NO: 233), 1017 (SEQ ID NO: 11), 1018 (SEQ ID NO: 12), 1019 (SEQ ID NO: 13), 1020 (SEQ ID NO: 234), 1040 (SEQ ID NO: 15), and 1530 (SEQ ID NO: 237) (Table 7) using template DNA generated with TempliPhi reagent.

[0195] The nucleic acid and amino acid sequences for the antibody are provided in Figure 13 O-R, where the bolded regions of the sequences highlight the CDRs, the underlined segment denotes a leader sequence added by PCR, and the shaded regions indicate the variable domain. The bolded regions of the sequences highlight the CDRs. Figure 14 O-R provides the nucleic acid and amino acid sequences for CDR and FWR regions for the antibody.

EXAMPLE 10

Development of codon optimized fully human IgG anti-SEB antibodies 79G9, 100C9, and 154G12

[0196] The complete open reading frames for the heavy and/or light chains of the fully human IgG anti-SEB antibodies 79G9, 100C9, and 154G12 were submitted to GeneArt AG (Regensburg, Germany) for codon usage optimization. Optimized forms of all three antibody (heavy and light chains) were sequenced. Light and heavy chain DNA inserts were sequenced with the following clone-specific sequencing primers listed in Table 7: 79G9 light chain - #1734 (SEQ ID NO: 244) and #1735 (SEQ ID NO: 245); 100C9 and 154G12 light chains - #1736 (SEQ ID NO: 246) and #1737 (SEQ ID NO: 247); 79G9, 100C9, and 154G12 heavy chains - #1730 (SEQ ID NO: 240), #1731 (SEQ ID NO: 241), #1732 (SEQ ID NO: 242), and #1733 (SEQ ID NO: 243). Sequencing was carried out using Beckman Coulter DTCS sequencing reagent followed by data acquisition and analysis on a Beckman Coulter CEQ2000.

[0197] The nucleic acid sequences for these antibodies are provided in Figure 15, where the bolded regions of the sequences highlight the CDRs, the underlined segment denotes a

leader sequence added by PCR, and the shaded regions indicate the antibody variable domain. Figure 16 provides the nucleic acid sequences for CDR and FWR regions for these antibodies.

EXAMPLE 11

Assessment of anti-SEB antibody-mediated inhibition of SEB-induced T-cell cytokine production

[0198] Human peripheral blood mononuclear cells (PBMCs) were used to determine the ability of the anti-SEB antibodies to inhibit SEB-induced T-cell cytokine production and measure their *in vitro* EC_{50} values. Approximately 1 X 10^5 PBMCs were cultured at 37°C in 5% CO_2 in 96-well flat-bottom tissue culture plates. Anti-SEB antibodies 79G9, 154G12, or a mixture of thereof, at 4x concentrations, were incubated with SEB (4x its *in vitro* ED_{50}) for 1 hour. The mixture was then added to the PBMCs (1x final concentration for both anti-SEB antibody and SEB) and incubated for 18-22 hours. To determine whether cytokine production occurred, supernatants were transferred to anti-IFN-γ and anti-TNF-α absorbed ELISA plates and assayed using an ELISA kit (R&D System) following the manufacturer's recommended procedure. EC_{50} calculations of anti-SEB antibody were performed using Prism4 (GraphPad Software). The sensitivity limit of the IFN-γ and TNF-α ELISA is 16 pg/mL. Results are shown in Table 9.

[0199] **Table 9.** EC_{50} values for Anti-SEB antibodies 154G12 and 79G9

Antibody (:g/ml)	IFN-(		TNF-∀	
	EC_{50} (ng/ml)	Std. Dev.	EC_{50} (ng/ml)	Std. Dev.
154G12 (1)	0.60	0.07	0.96	0.49
79G9 (10)	158.39	174.82	216.87	257.76
154G12(1), 79G9 (1)	0.90	0.21	1.23	0.52

EXAMPLE 12

Reactivity of SEB-specific antibodies 79G9, 100C9, and 154G12 to SEB-related toxins

To determine the SEB-specificity of antibodies 79G9, 100C9, and 154G12, these antibodies were examined for cross-reactivity to SEB-related Staphylococcus enterotoxins SEA, SED, SEC1, SEC2, and TSST-1; Streptococcal pyrogenic exotoxins SPE-A, SPE-B (each purchased from Toxin Technologies); and Tetanus toxoid (TT, purchased from Cylex Inc.). Each of the toxins was diluted to 0.5 μg/ml in coating buffer (50 mM carbonate-bicarbonate, pH 9.4 (Sigma)) and absorbed onto ELISA plates overnight at 4°C. The ELISA plates were blocked

with assay buffer (PBS (CellGro) containing 1% BSA (Sigma) and 0.05% Tween 20 (Bio-Rad)) for 2 hours at room temperature. The ELISA plates were washed once with washing buffer (PBS containing 0.05% Tween 20). Purified antibodies 79G9, 100C9, and 154G12; control mouse anti-TSST-1 (Hycult); and control mouse anti-TT (Abcam), each at a concentration of 2.5 μg/ml, were transferred into the ELISA plates at 100 μl per well and incubated at room temperature for 1 hour. Subsequently, plates were washed four times. Antibody binding was determined by adding 100 μl per well of horseradish peroxidase-conjugated goat anti-human IgG+M (H+L) (Jackson ImmunoResearch) diluted 1:10,000 in binding buffer was for antibodies 79G9, 100C9, and 154G12, while horseradish peroxidase-conjugated goat anti-mouse IgG (H+L) was used to detect control antibodies. Once added to the ELISA plates, horseradish peroxidase-conjugated antibodies were incubated at room temperature for 1 hour. Plates were washed four times and SureBlue substrate (Kirkegaard & Perry Laboratories) was added (100 μl/well) for 10 min. Reactions were stopped by adding 1 N sulfuric acid (50 μl/well), and the absorbance was determined at 450 nm. Results are shown in Figure 18.

[0200] *Biological Deposit of Antibody-Producing Cells:* Consistent with the detailed description and the written examples provided herein, examples of antibody-producing cells of the invention were deposited with the Amer. Type Cult. Coll. (10801 University Blvd., Manassas, Virginia 20110-2209). Hybridoma cell lines producing antibodies 100C9 and 79G9 were deposited January 3, 2007 and have been assigned ATCC accession numbers PTA-8115 and PTA-8116, respectively. Additionally, cells producing antibodies F10, F6, E12, C5, and 154G12 were deposited on December 19, 2007 and have been assigned ATCC Access. Nos. _____, _____, _____, _____, and _____, respectively.

[0201] The present invention is not limited to the embodiments described and exemplified above, but is capable of variation and modification within the scope of the appended claims.

What is Claimed:

1. An isolated human antibody that specifically binds to Staphylococcus enterotoxin B or an antigen-binding fragment thereof.

2. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO:68, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO:69, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 70.

3. The antibody of claim 2, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:56, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 58.

4. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 176.

5. The antibody of claim 4, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 174.

6. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 30.

7. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:56, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 58.

8. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 174.

9. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 28.

10. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO:130, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO:131, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 132.

11. The antibody of claim 10, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:104, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:105, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 106.

12. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 204.

13. The antibody of claim 12, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 200.

14. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 232.

15. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:104, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:105, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 106.

16. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 200.

17. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 186.

18. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO:92, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO:93, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 94.

19. The antibody of claim 18, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:80, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:81, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 82.

20. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 160.

21. The antibody of claim 20, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 158.

22. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 251

23. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:80, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:81, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 82.

24. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 158.

25. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 249.

26. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO:144, the heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO:146, and the heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 148.

27. The antibody of claim 26, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:136, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:138, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 140.

28. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 230.

29. The antibody of claim 28, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 228.

30. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 216.

31. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:136, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:138, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 140.

32. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 228.

33. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 214.

34. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the affinity of the antibody is less than about 3 X 10^{-8} M.

35. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the affinity of the antibody is less than about 1 X 10^{-9} M.

36. The antibody of claim 1, or an antigen-binding fragment thereof, wherein the affinity of the antibody is less than about 3 X 10^{-10} M.

37. A polynucleotide encoding the antibody or antigen-binding fragment of claim 1.

38. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 62, SEQ ID NO: 63, and SEQ ID NO: 64.

39. The polynucleotide of claim 38 comprising the nucleic acid sequences of SEQ ID NO: 50, SEQ ID NO: 51, and SEQ ID NO: 52.

40. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 175.

41. The polynucleotide of claim 40 comprising the nucleic acid sequence of SEQ ID NO: 173.

42. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 29.

43. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 50, SEQ ID NO: 51, and SEQ ID NO: 52.

44. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 173.

45. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 27.

46. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 123, SEQ ID NO: 124, and SEQ ID NO: 125 or the nucleic acid sequences of SEQ ID NO:194, SEQ ID NO:196, and SEQ ID NO:198.

47. The polynucleotide of claim 46 further comprising the nucleic acid sequences of SEQ ID NO: 98, SEQ ID NO: 99, and SEQ ID NO: 100 or the nucleic acid sequences of SEQ ID NO:180, SEQ ID NO:182, and SEQ ID NO:184.

48. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 203 or SEQ ID NO:172.

49. The polynucleotide of claim 48 further comprising the nucleic acid sequence of SEQ ID NO: 199 or SEQ ID NO: 171.

50. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 231 or SEQ ID NO:190.

51. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 98, SEQ ID NO: 99, and SEQ ID NO: 100 or the nucleic acid sequences of SEQ ID NO:180, SEQ ID NO:182, and SEQ ID NO:184.

52. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 199 or SEQ ID NO: 171.

53. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 185 or SEQ ID NO:189.

54. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 86, SEQ ID NO: 87, and SEQ ID NO: 88 or the nucleic acid sequences of SEQ ID NO:166, SEQ ID NO:168, and SEQ ID NO:170.

55. The polynucleotide of claim 54 further comprising the nucleic acid sequences of SEQ ID NO: 74, SEQ ID NO: 75, and SEQ ID NO: 76 or the nucleic acid sequences of SEQ ID NO:152, SEQ ID NO:154, and SEQ ID NO:156.

56. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 159 or SEQ ID NO:164.

57. The polynucleotide of claim 56 further comprising the nucleic acid sequence of SEQ ID NO: 157 or SEQ ID NO:150.

58. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 250 or SEQ ID NO:162.

59. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 74, SEQ ID NO: 75, and SEQ ID NO: 76 or the nucleic acid sequences of SEQ ID NO:152, SEQ ID NO:154, and SEQ ID NO:156.

60. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 157 or SEQ ID NO:150.

61. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 248 or SEQ ID NO:161.

62. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 253, SEQ ID NO: 255, and SEQ ID NO: 257 or the nucleic acid sequences of SEQ ID NO: 222, SEQ ID NO: 224, and SEQ ID NO:226.

63. The polynucleotide of claim 62 further comprising the nucleic acid sequences of SEQ ID NO: 259, SEQ ID NO: 261, and SEQ ID NO: 263 or the nucleic acid sequences of SEQ ID NO: 208, SEQ ID NO: 210, and SEQ ID NO: 212.

64. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 229 or SEQ ID NO:192.

65. The polynucleotide of claim 64 further comprising the nucleic acid sequence of SEQ ID NO: 227 or SEQ ID NO: 178.

66. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 215 or SEQ ID NO: 218.

67. The polynucleotide of claim 37 comprising the nucleic acid sequences of SEQ ID NO: 259, SEQ ID NO: 261, and SEQ ID NO: 263 or the nucleic acid sequences of SEQ ID NO: 208, SEQ ID NO: 210, and SEQ ID NO: 212.

68. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 227 or SEQ ID NO: 178.

69. The polynucleotide of claim 37 comprising the nucleic acid sequence of SEQ ID NO: 213 or SEQ ID NO: 217.

70. A composition comprising the antibody or antigen-binding fragment of claim 1 and a pharmaceutically acceptable carrier.

71. A vector comprising the polynucleotide sequence of claim 37.

72. A cell that expresses the antibody or antigen-binding fragment of claim 1.

73. The cell of claim 72, wherein the cell is a hybridoma.

74. A method for treating or preventing a Staphylococcus enterotoxin B-mediated disease in a subject, comprising administering to the subject a composition comprising a pharmaceutically acceptable carrier and at least one antibody, or an antigen-binding

fragment thereof, that specifically binds to Staphylococcus enterotoxin B in an amount effective to treat or prevent a Staphylococcus enterotoxin B-mediated disease.

75. The method of claim 74, wherein the antibody, or an antigen-binding fragment thereof, neutralizes the Staphylococcus enterotoxin B.

76. The method of claim 74, wherein the subject is a mammal.

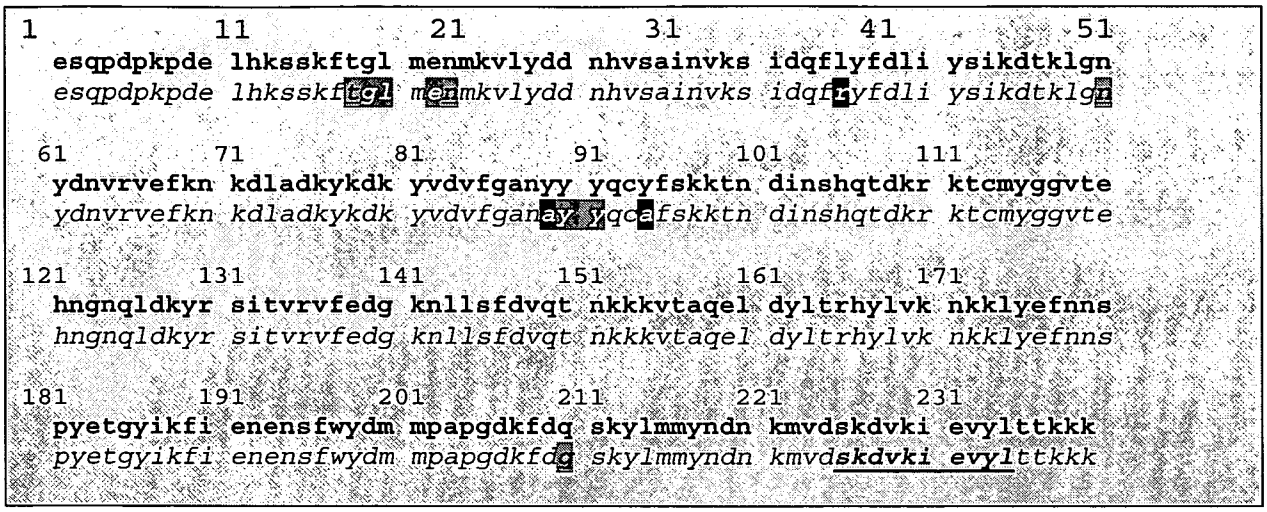
77. The method of claim 76, wherein the mammal is a human.

78. A method of making the antibody or antigen-binding of claim 1, comprising culturing a host cell under conditions suitable to produce the antibody or an antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell culture.

79. A method for neutralizing Staphylococcus enterotoxin B in a subject in need thereof, comprising administering to the subject at least one antibody or antigen-binding fragment, that specifically binds to and neutralizes Staphylococcus enterotoxin B in an amount effective to neutralize Staphylococcus enterotoxin B.

80. The method of claim 79, wherein the subject is a mammal.

81. The method of claim 80, wherein the mammal is a human.



SEB
SEB mutein vaccine
IVIG binding epitopes
TCR-binding H-bonds
TCR-binding Van der Waals contacts

Figure 1

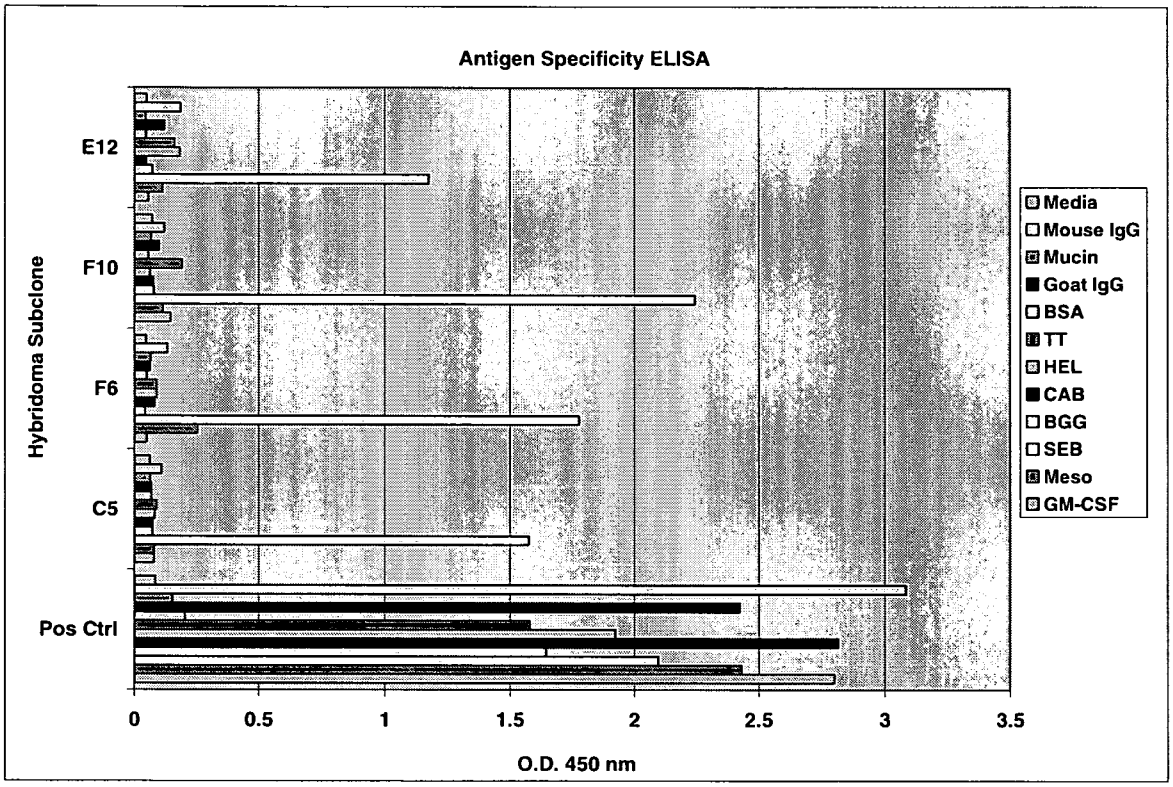

Antigen Specificity ELISA
Hybridoma Subclone
E12
F10
F6
C5
Pos Ctrl
0
0.5
1
1.5
2
2.5
3
3.5
O.D. 450 nm
Media
Mouse IgG
Mucin
Goat IgG
BSA
TT
HEL
CAB
BGG
SEB
Meso
GM-CSF

Figure 2

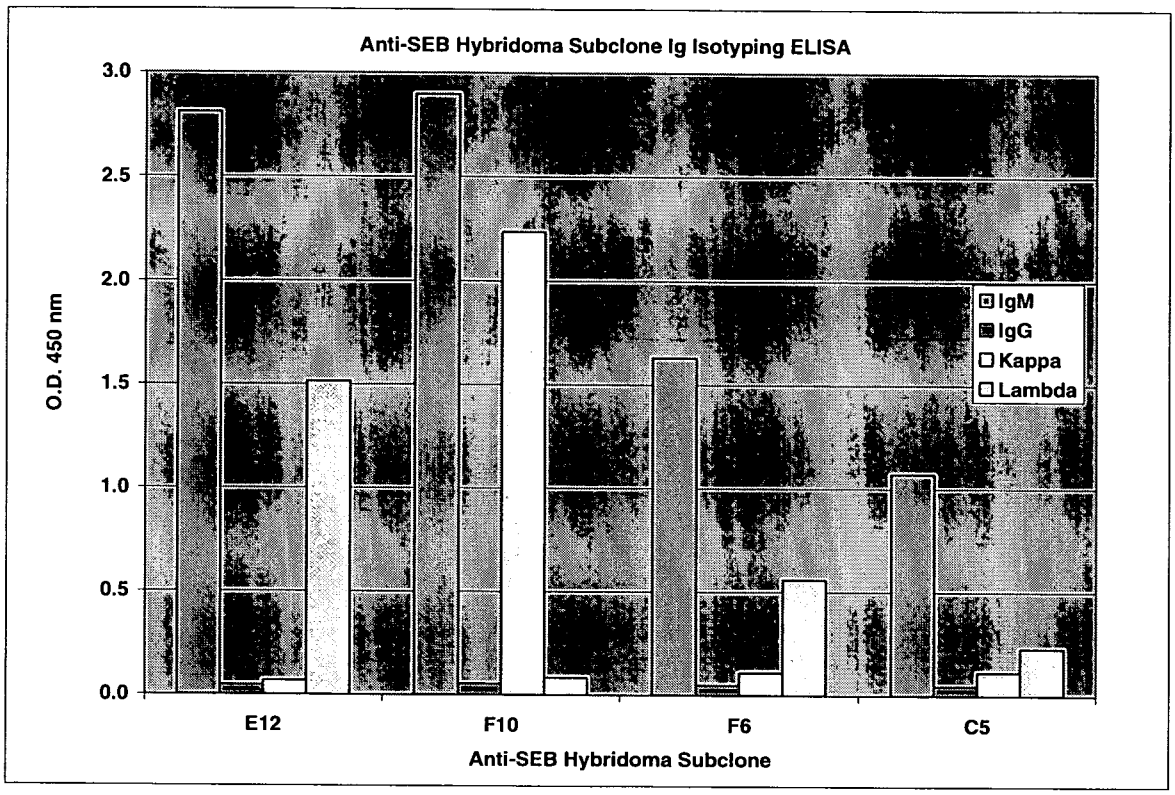

Anti-SEB Hybridoma Subclone Ig Isotyping ELISA
O.D. 450 nm
3.0
2.5
2.0
1.5
1.0
0.5
0.0
IgM
IgG
Kappa
Lambda
E12
F10
F6
C5
Anti-SEB Hybridoma Subclone

Figure 3

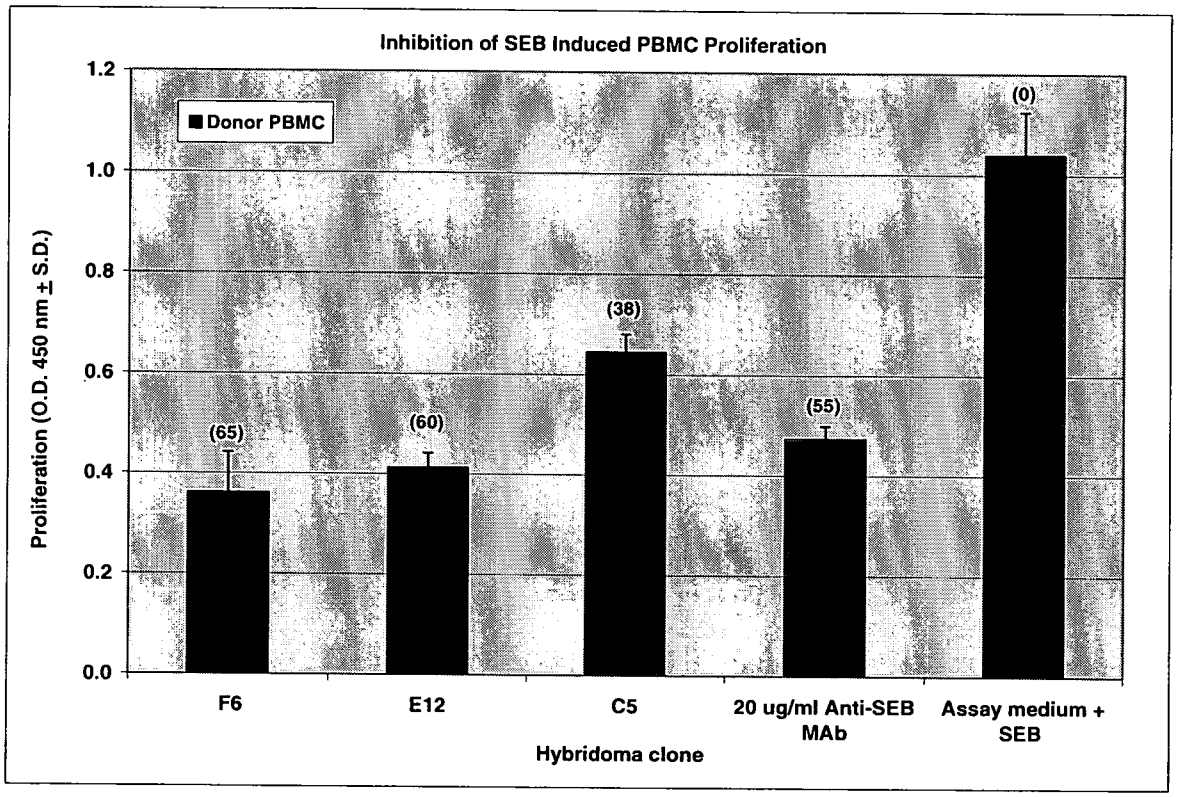

Inhibition of SEB Induced PBMC Proliferation
Donor PBMC
Proliferation (O.D. 450 nm ± S.D.)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
(65)
(60)
(38)
(55)
(0)
F6
E12
C5
20 ug/ml Anti-SEB MAb
Assay medium + SEB
Hybridoma clone

Figure 4

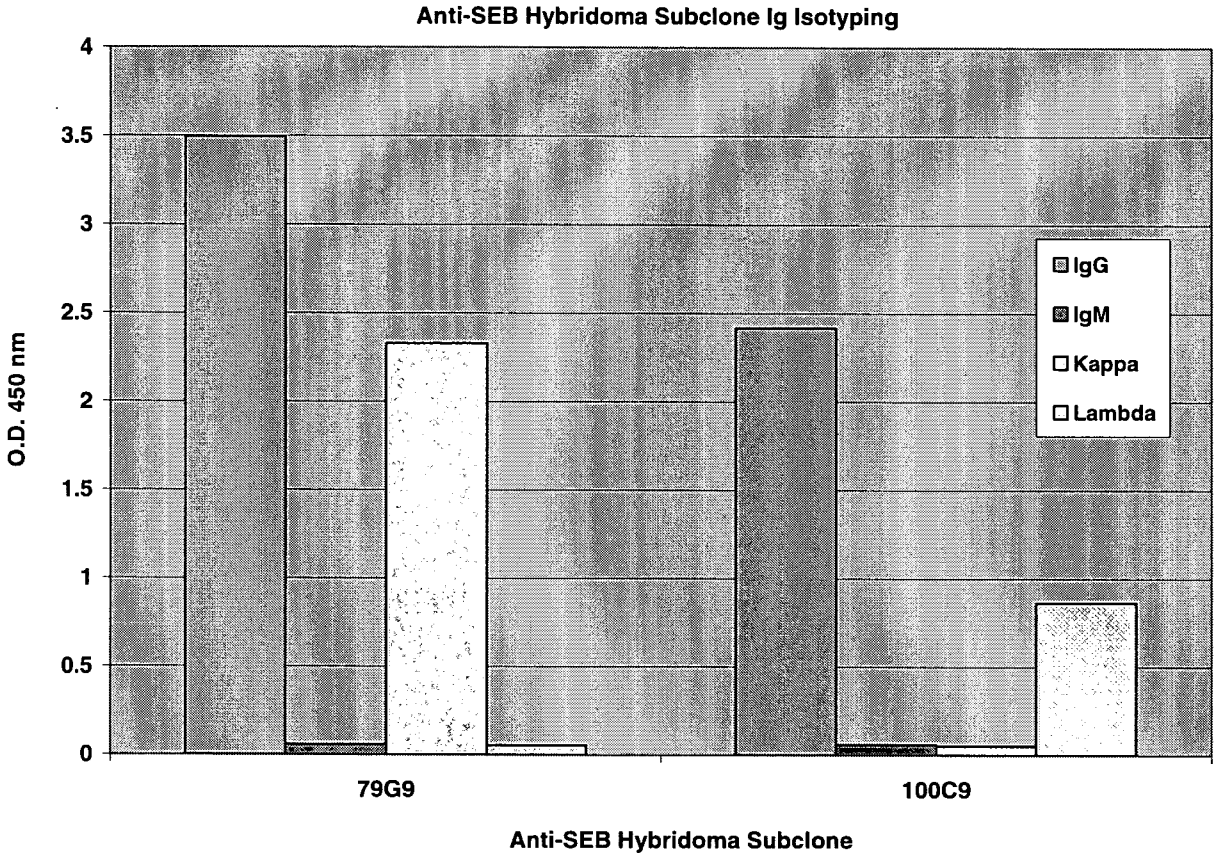

Anti-SEB Hybridoma Subclone Ig Isotyping
O.D. 450 nm
4
3.5
3
2.5
2
1.5
1
0.5
0
IgG
IgM
Kappa
Lambda
79G9
100C9
Anti-SEB Hybridoma Subclone

Figure 5

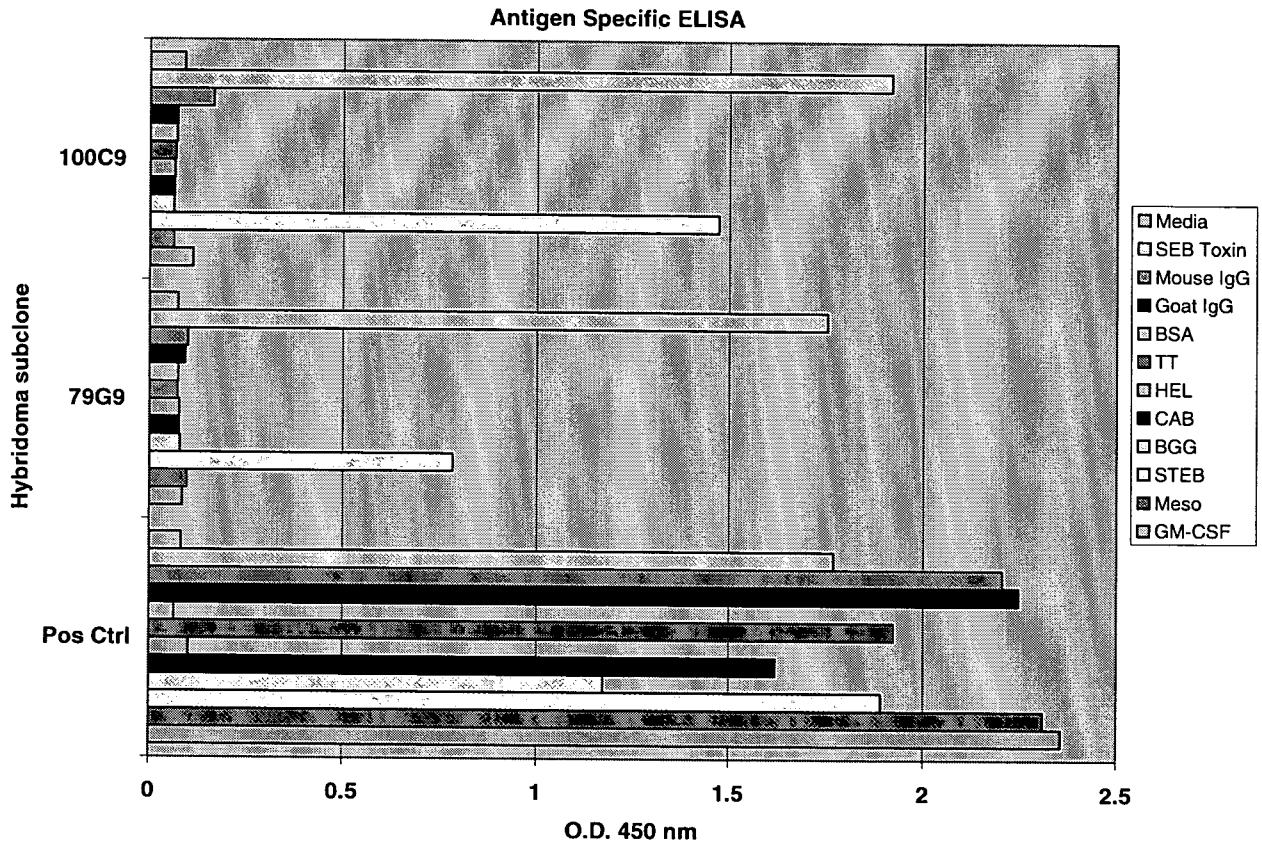

Antigen Specific ELISA
Hybridoma subclone
100C9
79G9
Pos Ctrl
0
0.5
1
1.5
2
2.5
O.D. 450 nm
Media
SEB Toxin
Mouse IgG
Goat IgG
BSA
TT
HEL
CAB
BGG
STEB
Meso
GM-CSF

Figure 6

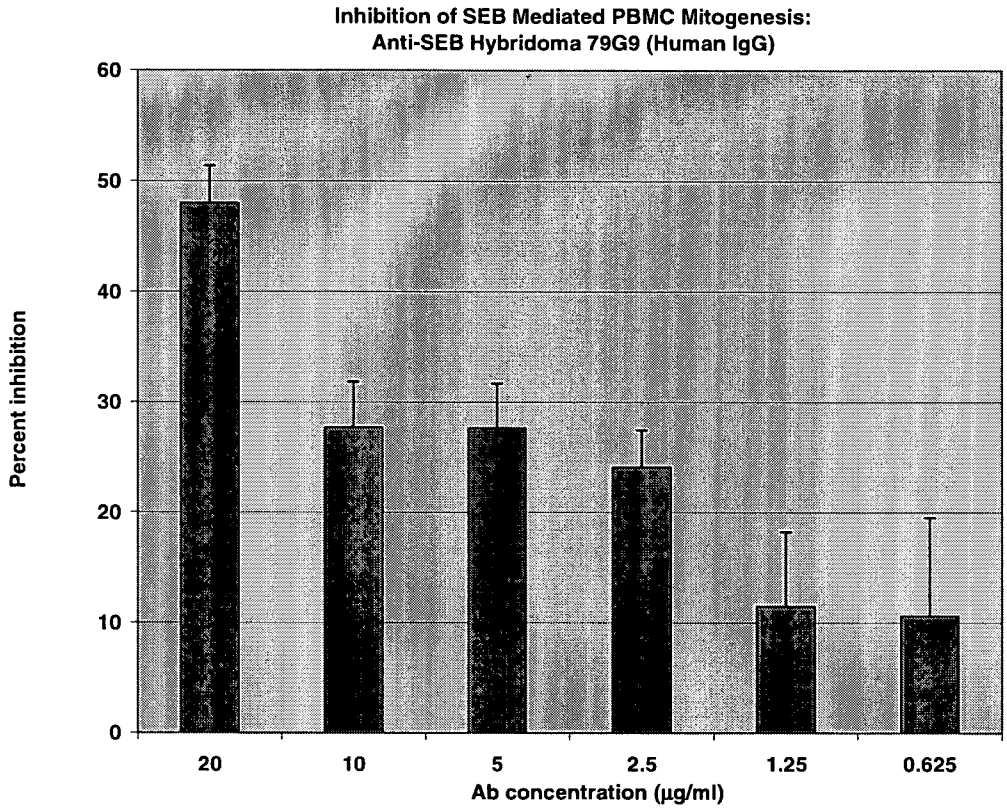

Inhibition of SEB Mediated PBMC Mitogenesis:
Anti-SEB Hybridoma 79G9 (Human IgG)
Percent inhibition
60
50
40
30
20
10
0
20
10
5
2.5
1.25
0.625
Ab concentration (µg/ml)

Figure 7

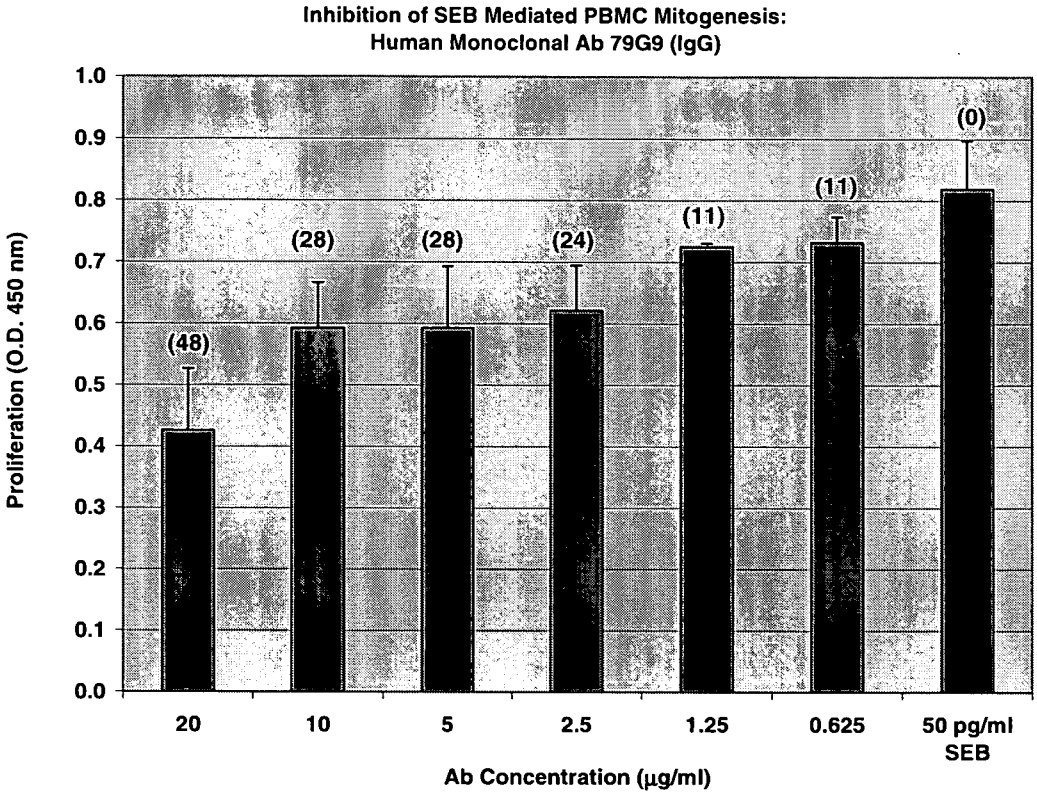
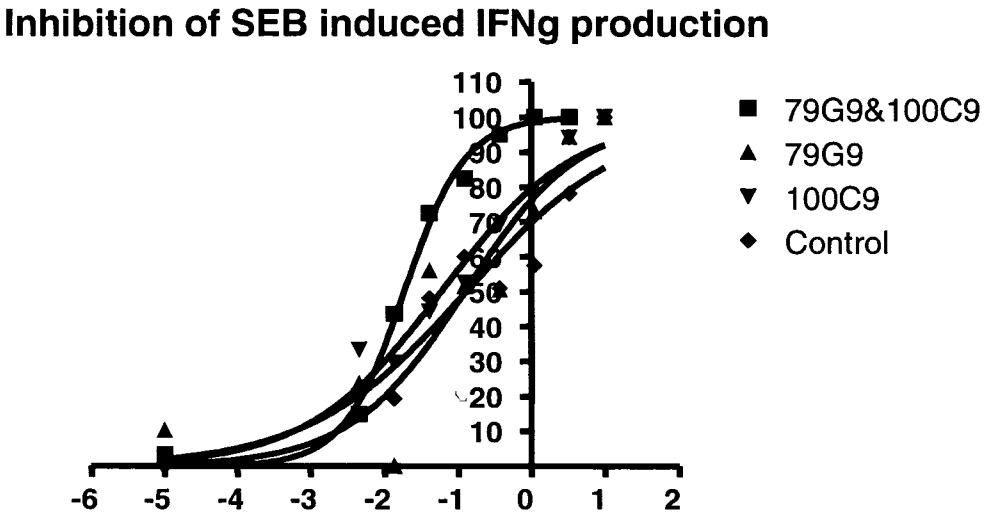
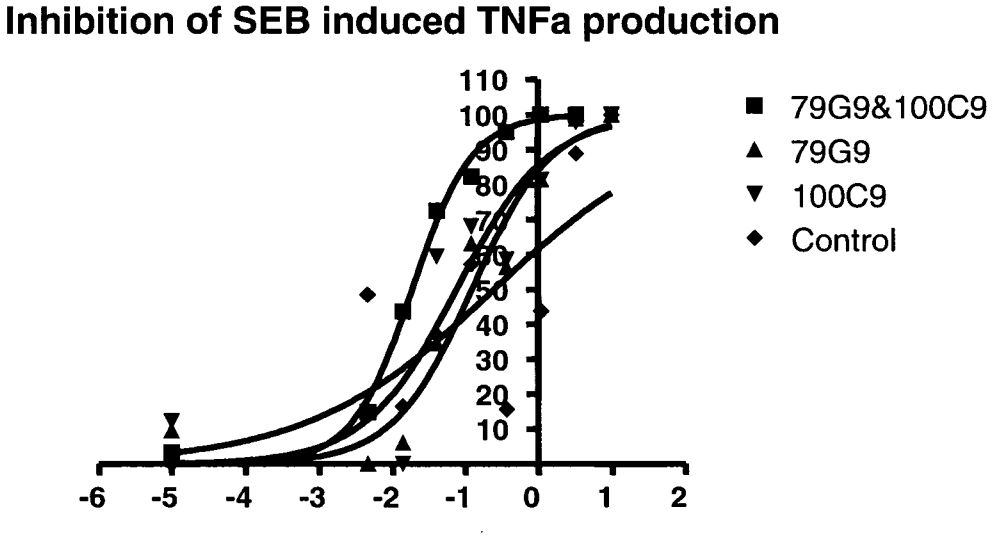

Inhibition of SEB Mediated PBMC Mitogenesis:
Human Monoclonal Ab 79G9 (IgG)
Proliferation (O.D. 450 nm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
(48)
(28)
(28)
(24)
(11)
(11)
(0)
20
10
5
2.5
1.25
0.625
50 pg/ml SEB
Ab Concentration (µg/ml)

Figure 8



	HILLSLOPE	EC50
79G9&100C9	1.048	0.01885
79G9	0.5545	0.1243
100C9	0.4779	0.05976
Contral	0.4080	0.1304

Figure 9



	HILLSLOPE	EC50
79G9&100C9	1.048	0.01885
79G9	0.7926	0.1250
100C9	0.6856	0.07665
Contral	0.3378	0.2517

Figure 10

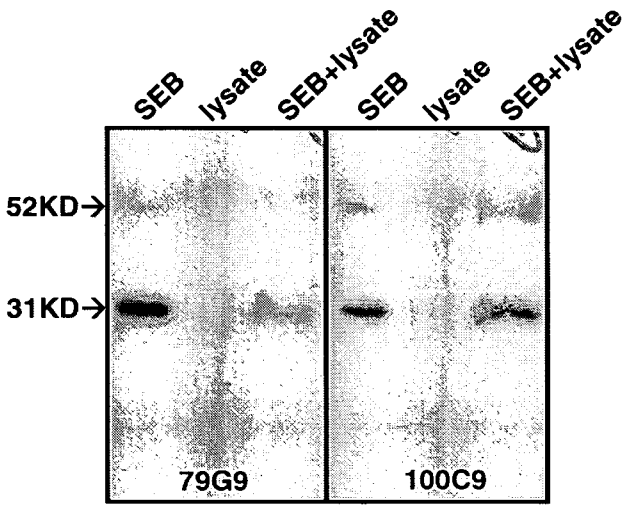

SEB
lysate
SEB+lysate
SEB
lysate
SEB+lysate
52KD
31KD
79G9
100C9

Figure 11

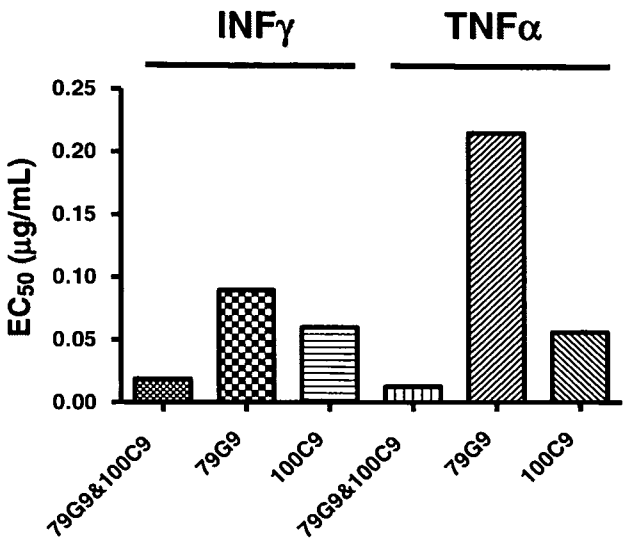

INFγ
TNFα
0.25
0.20
0.15
0.10
0.05
0.00
EC50 (μg/mL)
79G9&100C9
79G9
100C9
79G9&100C9
79G9
100C9

Figure 12

Figure 13A

F10: Light Chain Nucleotide Sequence: (SEQ ID NO:27)

GACGTTGAGCTGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGC**CGGGCCAGTCAGAGTATTAGTAGCTGGTTGGCC**TGGTAT
CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT**AAGGCGTCTAGTTTA**
GAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACT
CTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGT
ATAATAGTTATCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGA
ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA
GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTC
ACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG
AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG
GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

Figure 13B

F10 Light Chain Amino Acid Sequence: (SEQ ID NO: 28)

DVELTQSPSTLSASVGDRVTITC**RASQSISSWLA**WYQQKPGKAPKLLIY**KASSLESG**
VPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQ**YNSYPWT**FGQGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Figure 13C

F10: Heavy Chain Segment Including Variable Domain Nucleotide Sequence: (SEQ ID NO: 29)

CAGGTACAGCTGGTGCAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGA**TTCACCTTCAGTAGCTATAGCATGAACTGG**
GTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCA**TCCATTAGTAGTAGT**
AGTAGTTACATATACTACGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAG
AGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGA
CACGGCTGTGTATTACTGTGCGAGA**GGGGGGGTGGCTGGTCGAACCGAAATTT**
ACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTC
TCCTCAGGGAGTGCATCCGCCCCAACCCTTTTCCCCCTCGTCTCCTGTGAGAATTC
CCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCC
GACTCCATCACTTTCTCCTGGAAATACAAGAACAACTCTGACATCAGCAGCACCC
GGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGC
TGCTGCCTTCCAAGGACGTCATGCAGGGCACAGACGAACACGTGGTGTGCAAAG
TCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCA

Figure 13D

F10 Heavy Chain Segment Including Variable Domain Amino Acid Sequence: (SEQ ID NO: 30)

QVQLVQSGGGLVKPGGSLRLSCAASG**FTFSSYSMN**WVRQAPGKGLEWVS**SISSSSS**
YIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR**GGVAGRTEIYYYY**
YGMDVWGQGTTVTVSSGSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFS
WKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGN
KEKNVPLP

Figure 13E

100C9 Light Chain Nucleotide Sequence: (SEQ ID NO: 31)

ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTACACA
GCTCCTATGTGCTGACTCAGCCACCCTCGGTGTCGGTGTCCCCAGGACAGACGGC
CAGGATCACCTGC**TCTGGAGATGCATTGCCAAAGCAATATACTTATT**GGTACC
AGCAGAAGCCAGGCCAGGCCCCTGTGGTGGTGATCTAT**AAAGACAGTGAGAGG**
CCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAGCTCAGGGACAACAGTCACG
GTGACCATCAGTGGAGTCCAGGCAGAAGACGAGGCTGACTATTATTGT**CAATCA**
GCAGACAGCAGTGGTACTTCCCTGGTGTTCGGCGGAGGGACCAAGCTGACCGT
CCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAG
GAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGG
GAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGG
AGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTACC
TGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAAAAGCTACAGCTGCCAGGTCA
CGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATCTTCATAG

Figure 13F

100C9 Light Chain Amino Acid Sequence: (SEQ ID NO: 32)

MGWSCIILFLVATATGVHSSYVLTQPPSVSVSPGQTARITC**SGDALPKQYTYW**YQQ
KPGQAPVVVIY**KDSERPS**GIPERFSGSSSGTTVTVTISGVQAEDEADYYC**QSADSSGT**
SLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA
DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVA
PTESS*

Figure 13G

100C9 Heavy Chain Nucleotide Sequence: (SEQ ID NO: 33)

ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTACACA
GCGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCC
TGAGACTCTCCTGTTCAGCCTCTGGTTTCACCTTTAGTAGTTATTGGATGAGCT
GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGCCAACATAATACAA
GATGGAAGTGAGAAATACTATGCGGACTCTGTGAAGGGCCGGCTCACCATCT
CCAGAGACAACGCCAAGAACTCACTATATCTGCAGATGAACAGCCTGAGAGTCG
ACGACACGGCTGTGTATTATTGTGCGAGAGGATATGAGGGGTGTAGTGCAACC
AGGTGCTACCTGTACTACTTTGACTATTGGGGCCCGGGGACCCTGGTCACCGT
CTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG
AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG
AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCT
TCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGT
GCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC
AGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTGGTCCCCCATGCCCA
CCTTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTGTTCCCCCCAA
AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGT
GGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT
GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGT
ACCGTGTGGTCAGGGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGG
AGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCGGCCCCCATCGAGAAAACCA
TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCAT
CCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGGACA
ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAG
CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT
CTGGGTAAATGA

Figure 13H

100C9 Heavy Chain Amino Acid Sequence: (SEQ ID NO: 34)

MGWSCIILFLVATATGVHSEVQLVESGGGLVQPGGSLRLSCSAS**GFTFSSYWMS**WV
RQAPGKGLEWVA**NIIQDGSEKYYADSVKG**RLTISRDNAKNSLYLQMNSLRVDDTA
VYYCAR**GYEGCSATRCYLYYFDY**WGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGT
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSGPPCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVRVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPEDNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSLGK*

Figure 13I

79G9 Light Chain Nucleotide Sequence: (SEQ ID NO: 35)

ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTACACA
GCGACATTGAGTTGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTCGGAGACAG
AGTCGCCATCACTTGC**CGGGCCAGTCAGGGCATTAGCAATTATTTAGCC**TGGT
ATCAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT**GCTGCATTCGTTT**
TGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCA
CTCTCACAATCAGTAACCTGCAGCCTGAAGATTTTGCAACTTATTACTGT**CAACA**
ACTTAATAGTTATCCTCGCGCTTTCGGCCCTGGGACCAAAGTGGATATCAAACG
AACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA
TCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA
AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTG
TCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGC
TGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC
AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGA

Figure 13J

79G9 Light Chain Amino Acid Sequence: (SEQ ID NO: 36)

MGWSCIILFLVATATGVHSDIELTQSPSFLSASVGDRVAITC**RASQGISNYLA**WYQQ
KPGKAPKLLIY**AAFVLQS**GVPSRFSGSGSGTEFTLTISNLQPEDFATYYC**QQLNSYPR**
AFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA
LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGE*

Figure 13K

79G9+ Heavy Chain Nucleotide Sequence: (SEQ ID NO: 37)

ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTACACA
GCGAGGTGCAGCTGTTGCAGTCTGGCGCAGGACTGTTGAAGCCTTCGGAGACCCT
GTCCCTCACCTGCGCTGTCTAT**GGTGGGTCCTTCAGTGGATACTACTGGAGTT**
GGATCCGCCAGGCCCCAGGGAAGGGACTGGAGTGGATTGGG**GAAATCGATCAT**
AGTGGAACCACCAACTACAACCCGTCCCTCAAGAGTCGGGTCACCATATCAGT
AGAGACATCCAAGAACCAGTTCTCCCTGAGGCTGAGCTCTGTGACCGCCGCGGA
CTCGGCTGTCTATTACTGTGCGAGC**AGTGGATATTGTTCTCATGGTTTATGCCC**
CCAAGAGGACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAA
GGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACA
GCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGT
GGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTC
CTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGC
ACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC
AAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCA
GCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAG
CCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA
TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT
CAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG
CAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGC
CAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGA
GCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGAC
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GA

Figure 13L

79G9+Heavy Chain Amino Acid Sequence: (SEQ ID NO: 38)

MGWSCIILFLVATATGVHSEVQLLQSGAGLLKPSETLSLTCAVY**GGSFSGYYWS**WIR
QAPGKGLEWIG**EIDHSGTTNYNPSLKS**RVTISVETSKNQFSLRLSSVTAADSAVYYC
AS**SGYCSHGLCPQED**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK*

Figure 13M

79G9 Heavy Chain Nucleotide Sequence: (SEQ ID NO: 119)

ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTCCACT
CCGAGGTACAGCTGGAGGAGTCTGGCGCAGGACTGTTGAAGCCTTCGGAGACCC
TGTCCCTCACCTGCGCTGTCTATGGTGGGTCCTTCAGTGGATACTACTGGAGTT
GGATCCGCCAGGCCCCAGGGAAGGGACTGGAGTGGATTGGGGAAATCGATCAT
AGTGGAACCACCAACTACAACCCGTCCCTCAAGAGTCGGGTCACCATATCAGT
AGAGACATCCAAGAACCAGTTCTCCCTGAGGCTGAGCTCTGTGACCGCCGCGGA
CTCGGCTGTCTATTACTGTGCGAGCAGTGGATATTGTTCTCATGGTTTATGCCC
CCAAGAGGACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAA
GGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACA
GCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGT
GGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTC
CTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGC
ACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC
AAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCA
GCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAG
CCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA
TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT
CAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG
CAAGGTCTCCAACAAAGCCGTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGC
CAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGA
GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGAC
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GA

Figure 13N

79G9 Heavy Chain Amino Acid Sequence: (SEQ ID NO: 126)

MGWSCIILFLVATATGVHSEVQLEESGAGLLKPSETLSLTCAVY**GGSFSGYYWS**WIR
QAPGKGLEWIG**EIDHSGTTNYNPSLKS**RVTISVETSKNQFSLRLSSVTAADSAVYYC
AS**SGYCSHGLCPQED**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK
PSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKAVPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK*

Figure 13O

154G12 Light Chain Nucleotide Sequence (SEQ ID NO: 133)

ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTGCACT
CCCTATGTGCTGACTCAGCCACCCTCAGTGTCAGTGGCCCCAGGAGAGACGGCCA
GCATTCCTGT**GGGGGAAACAACATTGGAACTAAGAGTGTCCA**CTGGTACCAGC
AGAGGCCAGGCCAGGCCCCTCTACTGGTCCTCTAT**CATGACACCAGGCGGCCC**
TCAAGGATTCCTGAGCGATTCTCTGGCTCCAACTCTGGAAACACGGCCACCCTGA
CCATCAGCAGGGTCGAAGCCGGGGATGAGGCCGACTATTACTGT**CAGGTGTGG**
GATAGTCGAAGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCC
CAAGGCGGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCC
AACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACA
GTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACA
CCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACG
CCTGAGCAGTGGAAGTCCCACAAAAGCTACAGCTGCCAGGTCACGCATGAAGGG
AGCACCGTGGAGAAGACAGTGGCCCCTACAGAATCTTCATGA

Figure 13P

154G12 Light Chain Amino Acid Sequence (SEQ ID NO: 134)

MGWSCIILFLVATATGVHSLCADSATLSVSGPRRDGQHSC**GGNNIGTKSVH**WYQQR
PGQAPLLVLY**HDTRRPS**RIPERFSGSNSGNTATLTISRVEAGDEADYYC**QVWDSRRV**
FGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS
PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTE
SS*

Figure 13Q

154G12 Heavy Chain Nucleotide Sequence (SEQ ID NO: 141)

ATGGGATGGAGCTGTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTCCACT
CCCAGGTGCAGCTGTTGGAGTCAGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCC
TGAGACTCTCCTGTGCAGCCTCTGGATTCAGCTTTGGCGACTATTGGATGAGT
TGGGTCCGCCAGGCTCCAGGGAAGGGCCTGGAGTGGGTGGCCGACATAAAGC
CAGATGGCAGTGACAAAGACTATGTGGACTCTGTGAAGGGCCGATTCACCAT
CTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAGCAGCCTGCGAGG
CGAAGACACGGCTGTCTATTATTGTGCGAGAGACTATGTCGTCGTCGCACCAT
CTCAACCCCCAAACATTCACCCTGAATACTTCCAGAACTGGGGCCAGGGCACC
CTGGTCATCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAC
CCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGG
ACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCG
GCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG
AATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGAGCTGTGACAAAACT
CACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC
ATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGT
ACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCT
GAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACAC
CCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCT
GGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA
GCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTC
TTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC
TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCC
TCTCCCTGTCTCCGGGTAAATGA

Figure 13R

154G12 Heavy Chain Amino Acid Sequence (SEQ ID NO: 142)

MGWSCIILFLVATATGVHSQVQLLESGGGLVQPGGSLRLSCAASGFSFGDYWMSW
VRQAPGKGLEWVADIKPDGSDKDYVDSVKGRFTISRDNAKNSLYLQMSSLRGEDT
AVYYCARDYVVVAPSQPPNIHPEYFQNWGQGTLVIVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKRVSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK*

Figure 14A

F10 Light Chain Nucleotide Sequences:

FWR1:
GACGTTGAGCTGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGC (SEQ ID NO:47)

FWR2:
TGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT (SEQ ID NO:48)

FWR3:
GGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACC
ATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAG (SEQ ID NO:49)

CDR1:
CGGGCCAGTCAGAGTATTAGTAGCTGGTTGGCC (SEQ ID NO:50)

CDR2:
AAGGCGTCTAGTTTAGAAAGT (SEQ ID NO:51)

CDR3:
TATAATAGTTATCCGTGGACG (SEQ ID NO:52)

Figure 14B

F10 Light Chain Amino Acid Sequences:

FWR1:
DVELTQSPSTLSASVGDRVTITC (SEQ ID NO:53)

FWR2:
WYQQKPGKAPKLLIY (SEQ ID NO:54)

FWR3:
GVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQ (SEQ ID NO:55)

CDR1:
RASQSISSWLA (SEQ ID NO:56)

CDR2:
KASSLES (SEQ ID NO:57)

CDR3:
YNSYPWT (SEQ ID NO:58)

Figure 14C

F10 Heavy Chain Nucleotide Sequences

FWR1:
CAGGTACAGCTGGTGCAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGA (SEQ ID NO:59)

FWR2:
TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCA (SEQ ID NO:60)

FWR3:
CGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAAC
AGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGA (SEQ ID NO:61)

CDR1:
TTCACCTTCAGTAGCTATAGCATGAAC (SEQ ID NO:62)

CDR2:
TCCATTAGTAGTAGTAGTAGTTACATATACTACGCAGACTCAGTGAAGGGC (SEQ
ID NO:63)

CDR3:
GGGGGGGTGGCTGGTCGAACCGAAATTTACTACTACTACTACGGTATGGACGTC
(SEQ ID NO:64)

Figure 14D

F10 Heavy Chain Amino Acid Sequences:

FWR1:
QVQLVQSGGGLVKPGGSLRLSCAASG (SEQ ID NO:65)

FWR2:
WVRQAPGKGLEWVS (SEQ ID NO:66)

FWR3:
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:67)

CDR1:
FTFSSYSMN (SEQ ID NO:68)

CDR2:
SISSSSSYIYYADSVKG (SEQ ID NO:69)

CDR3:
GGVAGRTEIYYYYYGMDV (SEQ ID NO:70)

Figure 14E

100C9 Light Chain Nucleotide Sequences:

FWR1:
TCCTATGTGCTGACTCAGCCACCCTCGGTGTCGGTGTCCCCAGGACAGACGGCCA
GGATCACCTGC (SEQ ID NO:71)

FWR2:
TGGTACCAGCAGAAGCCAGGCCAGGCCCCTGTGGTGGTGATCTAT (SEQ ID
NO:72)

FWR3:
GGGATCCCTGAGCGATTCTCTGGCTCCAGCTCAGGGACAACAGTCACGGTGACC
ATCAGTGGAGTCCAGGCAGAAGACGAGGCTGACTATTATTGT (SEQ ID NO:73)

CDR1:
TCTGGAGATGCATTGCCAAAGCAATATACTTAT (SEQ ID NO:74)

CDR2:
AAAGACAGTGAGAGGCCCTCA (SEQ ID NO:75)

CDR3:
CAATCAGCAGACAGCAGTGGTACTTCCCTGGTG (SEQ ID NO:76)

Figure 14F

100C9 Light Chain Amino Acid Sequence

FWR1:
SYVLTQPPSVSVSPGQTARITC (SEQ ID NO:77)

FWR2:
WYQQKPGQAPVVVIY (SEQ ID NO:78)

FWR3:
GIPERFSGSSSGTTVTVTISGVQAEDEADYYC (SEQ ID NO:79)

CDR1:
SGDALPKQYTY (SEQ ID NO:80)

CDR2:
KDSERPS (SEQ ID NO:81)

CDR3:
QSADSSGTSLV (SEQ ID NO:82)

Figure 14G

100C9 Heavy Chain Nucleotide Sequences:

FWR1:
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTG
AGACTCTCCTGTTCAGCCTCT (SEQ ID NO:83)

FWR2:
TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGCC (SEQ ID NO:84)

FWR3:
CGGCTCACCATCTCCAGAGACAACGCCAAGAACTCACTATATCTGCAGATGAAC
AGCCTGAGAGTCGACGACACGGCTGTGTATTATTGTGCGAGA (SEQ ID NO:85)

CDR1:
GGTTTCACCTTTAGTAGTTATTGGATGAGC (SEQ ID NO:86)

CDR2:
AACATAATACAAGATGGAAGTGAGAAATACTATGCGGACTCTGTGAAGGGC
(SEQ ID NO:87)

CDR3:
GGATATGAGGGGTGTAGTGCAACCAGGTGCTACCTGTACTACTTTGACTAT
(SEQ ID NO:88)

Figure 14H

100C9 Heavy Chain Amino Acid Sequences:

FWR1:
EVQLVESGGGLVQPGGSLRLSCSAS (SEQ ID NO:89)

FWR2:
WVRQAPGKGLEWVA (SEQ ID NO:90)

FWR3:
RLTISRDNAKNSLYLQMNSLRVDDTAVYYCAR (SEQ ID NO:91)

CDR1:
GFTFSSYWMS (SEQ ID NO:92)

CDR2:
NIIQDGSEKYYADSVKG (SEQ ID NO:93)

CDR3:
GYEGCSATRCYLYYFDY (SEQ ID NO:94)

Figure 14I

79G9 Light Chain Nucleotide Sequences:

FWR1:
GACATTGAGTTGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTCGGAGACAGAG
TCGCCATCACTTGC (SEQ ID NO:95)

FWR2:
TGGTATCAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT (SEQ ID
NO:96)

FWR3:
GGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACA
ATCAGTAACCTGCAGCCTGAAGATTTTGCAACTTATTACTGT (SEQ ID NO:97)

CDR1:
CGGGCCAGTCAGGGCATTAGCAATTATTTAGCC (SEQ ID NO:98)

CDR2:
GCTGCATTCGTTTTGCAAAGT (SEQ ID NO:99)

CDR3:
CAACAACTTAATAGTTATCCTCGCGCT (SEQ ID NO:100)

Figure 14J

79G9 Light Chain Amino Acid Sequences:

FWR1:
DIELTQSPSFLSASVGDRVAITC (SEQ ID NO:101)

FWR2:
WYQQKPGKAPKLLIY (SEQ ID NO:102)

FWR3:
GVPSRFSGSGSGTEFTLTISNLQPEDFATYYC (SEQ ID NO:103)

CDR1:
RASQGISNYLA (SEQ ID NO:104)

CDR2:
AAFVLQS (SEQ ID NO:105)

CDR3:
QQLNSYPRA (SEQ ID NO:106)

Figure 14K

79G9+ Heavy Chain Nucleotide Sequences:

FWR1:
GAGGTGCAGCTGTTGCAGTCTGGCGCAGGACTGTTGAAGCCTTCGGAGACCCTGT
CCCTCACCTGCGCTGTCTAT (SEQ ID NO:107)

FWR2:
TGGATCCGCCAGGCCCCAGGGAAGGGACTGGAGTGGATTGGG (SEQ ID NO:108)

FWR3:
CGGGTCACCATATCAGTAGAGACATCCAAGAACCAGTTCTCCCTGAGGCTGAGCT
CTGTGACCGCCGCGGACTCGGCTGTCTATTACTGTGCGAGC (SEQ ID NO:109)

CDR1:
GGTGGGTCCTTCAGTGGATACTACTGGAGT (SEQ ID NO:110)

CDR2:
GAAATCGATCATAGTGGAACCACCAACTACAACCCGTCCCTCAAGAGT (SEQ ID
NO:111)

CDR3:
AGTGGATATTGTTCTCATGGTTTATGCCCCCAAGAGGAC (SEQ ID NO:112)

Figure 14L

79G9+ Heavy Chain Amino Acid Sequences:

FWR1:
EVQLLQSGAGLLKPSETLSLTCAVY (SEQ ID NO:113)

FWR2:
WIRQAPGKGLEWIG (SEQ ID NO:114)

FWR3:
RVTISVETSKNQFSLRLSSVTAADSAVYYCAS (SEQ ID NO:115)

CDR1:
GGSFSGYYWS (SEQ ID NO:116)

CDR2:
EIDHSGTTNYNPSLKS (SEQ ID NO:117)

CDR3:
SGYCSHGLCPQED (SEQ ID NO:118)

Figure 14M

79G9 Heavy Chain Nucleotide Sequences:

FWR1: (SEQ ID NO: 120)
GAGGTACAGCTGGAGGAGTCTGGCGCAGGACTGTTGAAGCCTTCGGAGACCCTG
TCCCTCACCTGCGCTGTCTAT

FWR2: (SEQ ID NO: 121)
TGGATCCGCCAGGCCCCAGGGAAGGGACTGGAGTGGATTGGG

FWR3: (SEQ ID NO: 122)
CGGGTCACCATATCAGTAGAGACATCCAAGAACCAGTTCTCCCTGAGGCTGAGCT
CTGTGACCGCCGCGGACTCGGCTGTCTATTACTGTGCGAGC

CDR1: (SEQ ID NO: 123)
GGTGGGTCCTTCAGTGGATACTACTGGAGT

CDR2: (SEQ ID NO: 124)
GAAATCGATCATAGTGGAACCACCAACTACAACCCGTCCCTCAAGAGT

CDR3: (SEQ ID NO: 125)
AGTGGATATTGTTCTCATGGTTTATGCCCCCAAGAGGAC

Figure 14N

79G9 Heavy Chain Amino Acid Sequences:

FWR1: (SEQ ID NO: 127)
EVQLEESGAGLLKPSETLSLTCAVY

FWR2: (SEQ ID NO: 128)
WIRQAPGKGLEWIG

FWR3: (SEQ ID NO: 129)
RVTISVETSKNQFSLRLSSVTAADSAVYYCAS

CDR1: (SEQ ID NO: 130)
GGSFSGYYWS

CDR2: (SEQ ID NO: 131)
EIDHSGTTNYNPSLKS

CDR3: (SEQ ID NO: 132)
SGYCSHGLCPQED

Figure 14O

154G12 Light Chain Nucleotide Sequences

FWR1: (SEQ ID NO: 258)
CTATGTGCTGACTCAGCCACCCTCAGTGTCAGTGGCCCCAGGAGAGACGGCCAG
CATTCCTGT

CRD1: (SEQ ID NO: 259)
GGGGGAAACAACATTGGAACTAAGAGTGTCCAC

FWR2: (SEQ ID NO: 260)
TGGTACCAGCAGAGGCCAGGCCAGGCCCCTCTACTGGTCCTCTAT

CDR2: (SEQ ID NO: 261)
CATGACACCAGGCGGCCCTCA

FWR3: (SEQ ID NO: 262)
TCAAGGATTCCTGAGCGATTCTCTGGCTCCAACTCTGGAAACACGGCCACCCTGA
CCATCAGCAGGGTCGAAGCCGGGGATGAGGCCGACTATTACTGT

CDR3: (SEQ ID NO: 263)
CAGGTGTGGGATAGTCGAAGGGTG

Figure 14P

154G12 Light Chain Amino Acid Sequences

FWR1:
LCADSATLSVSGPRRDGQHSC (SEQ ID NO: 135)

CDR1:
GGNNIGTKSVH (SEQ ID NO: 136)

FWR2:
WYQQRPGQAPLLVLY (SEQ ID NO: 137)

CDR2:
HDTRRPS (SEQ ID NO: 138)

FWR3:
RIPERFSGSNSGNTATLTISRVEAGDEADYYC (SEQ ID NO: 139)

CDR3:
QVWDSRRV (SEQ ID NO: 140)

Figure 14Q

154G12 Heavy Chain Nucleotide Sequences

FWR1: (SEQ ID NO: 252)
CAGGTGCAGCTGTTGGAGTCAGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCT

CDR1: (SEQ ID NO: 253)
GGATTCAGCTTTGGCGACTATTGGATGAGT

FWR2: (SEQ ID NO: 254)
TGGGTCCGCCAGGCTCCA

CDR2: (SEQ ID NO: 255)
GGGAAGGGCCTGGAGTGGGTGGCCGACATAAAGCCAGATGGCAGTGACAAAGA
CTATGTGGACTCTGTGAAGGGC

FWR3: (SEQ ID NO: 256)
CGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAGC
AGCCTGCGAGGCGAAGACACGGCTGTCTATTATTGTGCGAGA

CDR3: (SEQ ID NO: 257)
GACTATGTCGTCGTCGCACCATCTCAACCCCCAAACATTCACCCTGAATACTTCC
AGAAC

Figure 14R

154G12 Heavy Chain Amino Acid Sequences

FWR1:
QVQLLESGGGLVQPGGSLRLSCAAS (SEQ ID NO: 143)

CDR1:
GFSFGDYWMS (SEQ ID NO: 144)

FWR2:
WVRQAPGKGLEWVA (SEQ ID NO: 145)

CDR2:
DIKPDGSDKDYVDSVKG (SEQ ID NO: 146)

FWR3:
RFTISRDNAKNSLYLQMSSLRGEDTAVYYCAR (SEQ ID NO: 147)

CDR3:
DYVVVAPSQPPNIHPEYFQN (SEQ ID NO: 148)

Figure 15A

100C9 Codon Optimized Light Chain Nucleotide Sequence (SEQ ID NO: 149)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCACT
CCTCCTACGTGCTGACCCAGCCTCCTTCCGTGTCCGTGTCCCCTGGCCAGACCGCC
CGGATCACCTGC**TCCGGCGACGCCCTGCCTAAGCAGTACACCTAC**TGGTATCA
GCAGAAGCCCGGCCAGGCCCCTGTGGTGGTGATCTAC**AAGGACTCCGAGCGGC**
CTTCCGGCATCCCTGAGCGGTTCTCCGGCTCCTCCTCCGGCACCACCGTGACCGT
GACCATCTCCGGCGTGCAGGCCGAGGACGAGGCCGACTACTACTGC**CAGTCCGC**
CGACTCCAGCGGCACCTCCCTGGTGTTTGGCGGCGGAACAAAGCTGACCGTGC
TGGGCCAGCCTAAGGCCGCTCCCTCCGTGACCCTGTTCCCTCCTTCCTCCGAGGA
ACTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCTCCGACTTCTACCCTGGC
GCTGTGACCGTGGCCTGGAAGGCTGACTCCTCCCCTGTGAAGGCCGGCGTGGAG
ACAACCACCCCTTCCAAGCAGTCCAACAACAAGTACGCCGCCTCCTCCTACCTGT
CCCTGACCCCTGAGCAGTGGAAGTCCCACAAGTCCTACAGCTGCCAGGTGACCC
ACGAGGGCTCCACCGTGGAAAAGACCGTGGCCCCTACCGAGTCCTCCTGA

Figure 15B

100C9 Codon Optimized Heavy Chain Nucleotide Sequence (SEQ ID NO: 163)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCACT
CCGAGGTGCAGCTGGTCGAGTCTGGCGGCGGACTGGTGCAGCCTGGCGGCTCCC
TGCGGCTGTCCTGCTCCGCCTCCGGCTTCACCTTCTCCTCCTACTGGATGTCCT
GGGTGCGGCAGGCTCCTGGCAAGGGCCTGGAGTGGGTGGCCAACATCATCCAG
GACGGCTCCGAGAAGTACTACGCCGACTCCGTGAAGGGCCGGCTGACCATCT
CCCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTCCCTGCGGGTGG
ACGACACCGCCGTGTACTACTGCGCCAGGGGCTACGAGGGCTGCTCCGCCACC
CGGTGCTACCTGTACTACTTCGACTACTGGGGCCCTGGCACCCTGGTGACCGT
GTCCTCCGCCTCCACCAAGGGCCCTTCCGTGTTCCCTCTGGCCCCTTCCTCCAAGT
CCACCTCCGGCGGCACCGCCGCTCTGGGCTGCCTGGTGAAGGACTACTTCCCTGA
GCCTGTGACCGTGAGCTGGAACTCTGGCGCCCTGACCAGCGGCGTGCACACCTTC
CCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACAGTGCC
TTCCTCCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCTTCC
AACACCAAGGTGGACAAGCGGGTGGAGCCTAAGTCCGGCCCTCCTTGCCCTCCCT
GCCCTGCCCCTGAGCTGCTGGGCGGACCCTCCGTGTTCCTGTTCCCTCCTAAGCCT
AAGGACACCCTGATGATCTCCCGGACCCCTGAGGTGACCTGCGTGGTGGTGGAC
GTGTCCCACGAGGATCCTGAGGTGAAGTTCAATTGGTACGTGGACGGCGTGGAG
GTGCACAACGCTAAGACCAAGCCTCGGGAGGAACAGTACAACTCCACCTACCGG
GTGGTGCGGGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATAC
AAGTGCAAGGTCTCCAACAAGGCTCTGCCTGCCCCCATCGAAAAGACCATCTCCA
AGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCCCCCAGCCGGG
AGGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACC
CTTCCGATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCTGAGGACAACTACA
AGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCAAGCTG
ACCGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGC
ACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGTCTCTGGGCAA
GTGA

Figure 15C

79G9 Codon Optimized Light Chain Nucleotide Sequence (SEQ ID NO: 177)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCACT
CCGACATCGAGCTGACCCAGTCCCCCTCCTTCCTGTCCGCCTCCGTGGGCGACCG
GGTGGCCATCACCTGCCGGGCCTCCCAGGGCATCTCCAACTACCTGGCCTGGT
ATCAGCAGAAGCCTGGCAAGGCCCCTAAGCTGCTGATCTACGCCGCCTTCGTGC
TGCAGTCCGGCGTGCCTTCCCGGTTCTCCGGCTCCGGCAGCGGCACCGAGTTCA
CCCTGACCATCTCCAACCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCA
GCTGAACTCCTACCCTCGGGCCTTCGGCCCTGGCACCAAGGTGGACATCAAGC
GGACCGTGGCCGCTCCTTCCGTGTTCATCTTCCCTCCCTCCGACGAGCAGCTGAA
GTCCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGGAGGCC
AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACTCCCAGGAATCC
GTCACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCC
TGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACC
AGGGCCTGTCCAGCCCTGTGACCAAGTCCTTCAACCGGGGCGAGTGA

Figure 15D

79G9 Codon Optimized Heavy Chain Nucleotide Sequence (SEQ ID NO: 191)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCACT
CCGAGGTGCAGCTGGAGGAATCCGGCGCTGGCCTGCTGAAGCCTTCCGAGACAC
TGTCCCTGACCTGCGCCGTGTACGGCGGCTCCTTCTCCGGCTACTACTGGTCC
TGGATCCGGCAGGCTCCTGGCAAGGGCCTGGAGTGGATCGGCGAGATCGACCA
CTCCGGCACCACCAACTACAACCCTTCCCTGAAGTCCCGGGTGACCATCTCCG
TGGAGACATCCAAGAACCAGTTCTCCCTGCGGCTGTCCTCCGTGACCGCCGCTGA
CTCCGCCGTGTACTACTGCGCCTCCAGCGGCTACTGCTCCCACGGCCTGTGCC
CTCAGGAAGATTGGGGCCAGGGCACCCTGGTGACCGTGTCCTCCGCCTCCACCA
AGGGCCCTTCCGTGTTCCCTCTGGCCCCTTCCTCCAAGTCCACCTCCGGCGGCACC
GCCGCTCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAGCCTGTGACCGTGAGCT
GGAACTCTGGCGCTCTGACCAGCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTC
CTCCGGCCTGTACTCCCTGTCCAGCGTGGTGACAGTGCCTTCCTCCTCCCTGGGCA
CCCAGACCTACATCTGCAACGTGAACCACAAGCCTTCCAACACCAAGGTGGACA
AGCGGGTGGAGCCTAAGTCCTGCGACAAGACCCACACCTGCCCTCCCTGCCCTGC
CCCTGAGCTGCTGGGCGGACCCTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGAC
ACCCTGATGATCTCCCGGACCCCTGAGGTGACCTGCGTGGTGGTGGACGTGTCCC
ACGAGGATCCTGAGGTGAAGTTCAATTGGTACGTGGACGGCGTGGAGGTGCACA
ACGCCAAGACCAAGCCTCGGGAGGAACAGTACAACTCCACCTACCGGGTGGTGT
CCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCA
AGGTCTCCAACAAGGCCGTGCCTGCCCCTATCGAAAAGACCATCTCCAAGGCCA
AGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTAGCCGGGAGGAAA
TGACCAAGAATCAGGTGTCCCTGACATGTCTGGTGAAGGGCTTCTACCCTTCCGA
TATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCAC
CCCTCCTGTGCTGGACTCCGACGGCAGCTTCTTCCTGTACTCCAAGCTGACCGTG
GACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAG
GCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGTCTCCTGGCAAGTGA

Figure 15E

154G12 Codon Optimized Light Chain Nucleotide Sequence (SEQ ID NO: 205)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCACT
CCCTGTGCGCCGACTCCGCCACCCTGTCCGTGTCCGGCCCTCGGAGGGACGGCCA
GCACTCCTGC**GGCGGCAACAACATCGGCACCAAGTCCGTGCAC**TGGTATCAG
CAGCGGCCTGGACAGGCCCCTCTGCTGGTGCTGTAC**CACGACACCAGGCGGCC**
TTCCCGGATCCCTGAGCGGTTCTCCGGCTCCAACTCCGGCAACACCGCTACCCTG
ACCATCTCCCGGGTGGAGGCCGGCGACGAGGCCGACTACTACTGC**CAGGTGTGG**
GACTCCAGGCGGGTGTTCGGCGGAGGAACAAAGCTGACCGTGCTGGGCCAGCC
TAAGGCCGCTCCTTCCGTGACCCTGTTCCCTCCTTCCTCCGAGGAACTGCAGGCC
AACAAGGCCACCCTGGTGTGCCTGATCTCCGACTTCTACCCTGGCGCCGTGACCG
TGGCTTGGAAGGCCGACTCCTCCCCTGTGAAGGCTGGCGTGGAGACAACCACCC
CTTCCAAGCAGTCCAACAACAAGTACGCCGCCTCCTCCTACCTGTCCCTGACCCC
TGAGCAGTGGAAGTCCCACAAGTCCTACAGCTGCCAGGTGACCCACGAGGGCTC
CACCGTGGAAAAGACCGTGGCCCCTACCGAGTCCTCCTGA

Figure 15F

154G12 Codon Optimized Heavy Chain Nucleotide Sequence (SEQ ID NO: 219)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGCACT
CCCAGGTGCAGCTGCTGGAGTCTGGCGGCGGACTGGTGCAGCCTGGCGGCTCCCT
GCGGCTGTCCTGCGCCGCCTCCGGCTTCTCCTTCGGCGACTACTGGATGTCCT
GGGTGCGGCAGGCTCCTGGCAAGGGCCTGGAGTGGGTGGCCGACATCAAGCCT
GACGGCAGCGACAAGGACTACGTGGACTCCGTGAAGGGCCGGTTCACCATCT
CCCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGTCCTCCCTGCGGGCG
AGGACACCGCCGTGTACTACTGCGCCAGAGACTACGTGGTGGTGGCCCCTTCC
CAGCCTCCTAACATCCACCCTGAGTACTTCCAGAACTGGGGCCAGGGCACCCT
GGTGATCGTGTCCTCCGCCTCCACCAAGGGCCCTTCCGTGTTCCCTCTGGCCCCCT
CCTCCAAGTCCACCTCCGGCGGCACCGCCGCTCTGGGCTGCCTGGTGAAGGACTA
CTTCCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCCCTGACCAGCGGAGTG
CACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTGGT
GACCGTGCCTTCCTCCTCCCTGGGCACCCAGACCTACATCTGCAACGTGAACCAC
AAGCCTTCCAACACCAAGGTGGACAAGCGGGTGTCCTGCGACAAGACCCACACC
TGCCCTCCCTGCCCTGCCCCTGAGCTGCTGGGCGGACCCTCCGTGTTCCTGTTCCC
TCCTAAGCCTAAGGACACCCTGATGATCTCCCGGACCCCTGAGGTGACCTGTGTG
GTGGTGGACGTGTCCCACGAGGATCCTGAGGTGAAGTTCAATTGGTACGTGGAC
GGCGTGGAGGTGCACAACGCTAAGACCAAGCCTCGGGAGGAACAGTACAACTCC
ACCTACCGGGTGGTGTCTGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCA
AGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCCGCTCCCATCGAAAAGA
CCATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCCCC
CAGCCGGGAGGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGG
CTTCTACCCTTCCGATATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCTGAGAAC
AACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTC
CAAGCTGACCGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCC
GTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCC
CTGGCAAGTGA

Figure 16A

100C9 Codon Optimized Light Chain Nucleotide Sequences

FWR1:
TCCTACGTGCTGACCCAGCCTCCTTCCGTGTCCGTGTCCCCTGGCCAGACCGCCC
GGATCACCTGC (SEQ ID NO:151)

CDR1:
TCCGGCGACGCCCTGCCTAAGCAGTACACCTAC (SEQ ID NO:152)

FWR2:
TGGTATCAGCAGAAGCCCGGCCAGGCCCCTGTGGTGGTGATCTAC (SEQ ID
NO:153)

CDR2:
AAGGACTCCGAGCGGCCTTCC (SEQ ID NO:154)

FWR3:
GGCATCCCTGAGCGGTTCTCCGGCTCCTCCTCCGGCACCACCGTGACCGTGACCA
TCTCCGGCGTGCAGGCCGAGGACGAGGCCGACTACTACTGC (SEQ ID NO:155)

CDR3:
CAGTCCGCCGACTCCAGCGGCACCTCCCTGGTG (SEQ ID NO:156)

Figure 16B

100C9 Codon Optimized Heavy Chain Nucleotide Sequences

FWR1:
GAGGTGCAGCTGGTCGAGTCTGGCGGCGGACTGGTGCAGCCTGGCGGCTCCCTG
CGGCTGTCCTGCTCCGCCTCC (SEQ ID NO: 165)

CDR1:
GGCTTCACCTTCTCCTCCTACTGGATGTCC (SEQ ID NO: 166)

FWR2:
TGGGTGCGGCAGGCTCCTGGCAAGGGCCTGGAGTGGGTGGCC (SEQ ID NO: 167)

CDR2:
AACATCATCCAGGACGGCTCCGAGAAGTACTACGCCGACTCCGTGAAGGGC
(SEQ ID NO: 168)

FWR3:
CGGCTGACCATCTCCCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACT
CCCTGCGGGTGGACGACACCGCCGTGTACTACTGCGCCAGG (SEQ ID NO: 169)

CDR3:
GGCTACGAGGGCTGCTCCGCCACCCGGTGCTACCTGTACTACTTCGACTAC (SEQ
ID NO: 170)

Figure 16C

79G9 Codon Optimized Light Chain Nucleotide Sequences

FWR1:
GACATCGAGCTGACCCAGTCCCCCTCCTTCCTGTCCGCCTCCGTGGGCGACCGGG
TGGCCATCACCTGC (SEQ ID NO: 179)

CDR1:
CGGGCCTCCCAGGGCATCTCCAACTACCTGGCC (SEQ ID NO: 180)

FWR2:
TGGTATCAGCAGAAGCCTGGCAAGGCCCCTAAGCTGCTGATCTAC (SEQ ID
NO:181)

CDR2:
GCCGCCTTCGTGCTGCAGTCC (SEQ ID NO:182)

FWR3:
GGCGTGCCTTCCCGGTTCTCCGGCTCCGGCAGCGGCACCGAGTTCACCCTGACCA
TCTCCAACCTGCAGCCTGAGGACTTCGCCACCTACTACTGC (SEQ ID NO:183)

CDR3:
CAGCAGCTGAACTCCTACCCTCGGGCC (SEQ ID NO:184)

Figure 16D

79G9 Codon Optimized Heavy Chain Nucleotide Sequences

FWR1:
GAGGTGCAGCTGGAGGAATCCGGCGCTGGCCTGCTGAAGCCTTCCGAGACACTG
TCCCTGACCTGCGCCGTGTAC (SEQ ID NO:193)

CDR1:
GGCGGCTCCTTCTCCGGCTACTACTGGTCC (SEQ ID NO:194)

FWR2:
TGGATCCGGCAGGCTCCTGGCAAGGGCCTGGAGTGGATCGGC (SEQ ID NO:195)

CDR2:
GAGATCGACCACTCCGGCACCACCAACTACAACCCTTCCCTGAAGTCC (SEQ ID
NO:196)

FWR3:
CGGGTGACCATCTCCGTGGAGACATCCAAGAACCAGTTCTCCCTGCGGCTGTCCT
CCGTGACCGCCGCTGACTCCGCCGTGTACTACTGCGCCTCC (SEQ ID NO:197)

CDR3:
AGCGGCTACTGCTCCCACGGCCTGTGCCCTCAGGAAGAT (SEQ ID NO:198)

Figure 16E

154G12 Codon Optimized Light Chain Nucleotide Sequences

FWR1:
CTGTGCGCCGACTCCGCCACCCTGTCCGTGTCCGGCCCTCGGAGGGACGGCCAGC ACTCCTGC (SEQ ID NO: 207)

CDR1:
GGCGGCAACAACATCGGCACCAAGTCCGTGCAC (SEQ ID NO: 208)

FWR2:
TGGTATCAGCAGCGGCCTGGACAGGCCCCTCTGCTGGTGCTGTAC (SEQ ID NO: 209)

CDR2:
CACGACACCAGGCGGCCTTCC (SEQ ID NO: 210)

FWR3:
CGGATCCCTGAGCGGTTCTCCGGCTCCAACTCCGGCAACACCGCTACCCTGACCA TCTCCCGGGTGGAGGCCGGCGACGAGGCCGACTACTACTGC (SEQ ID NO: 211)

CDR3:
CAGGTGTGGGACTCCAGGCGGGTG (SEQ ID NO: 212)

Figure 16F

154G12 Codon Optimized Heavy Chain Nucleotide Sequences

FWR1:
CAGGTGCAGCTGCTGGAGTCTGGCGGCGGACTGGTGCAGCCTGGCGGCTCCCTG
CGGCTGTCCTGCGCCGCCTCC (SEQ ID NO: 221)

CDR1:
GGCTTCTCCTTCGGCGACTACTGGATGTCC (SEQ ID NO: 222)

FWR2:
TGGGTGCGGCAGGCTCCTGGCAAGGGCCTGGAGTGGGTGGCC (SEQ ID NO: 223)

CDR2:
GACATCAAGCCTGACGGCAGCGACAAGGACTACGTGGACTCCGTGAAGGGC
(SEQ ID NO: 224)

FWR3:
CGGTTCACCATCTCCCGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGTCCT
CCCTGCGGGGCGAGGACACCGCCGTGTACTACTGCGCCAGA (SEQ ID NO: 225)

CDR3:
GACTACGTGGTGGTGGCCCCTTCCCAGCCTCCTAACATCCACCCTGAGTACTTCC
AGAAC (SEQ ID NO: 226)

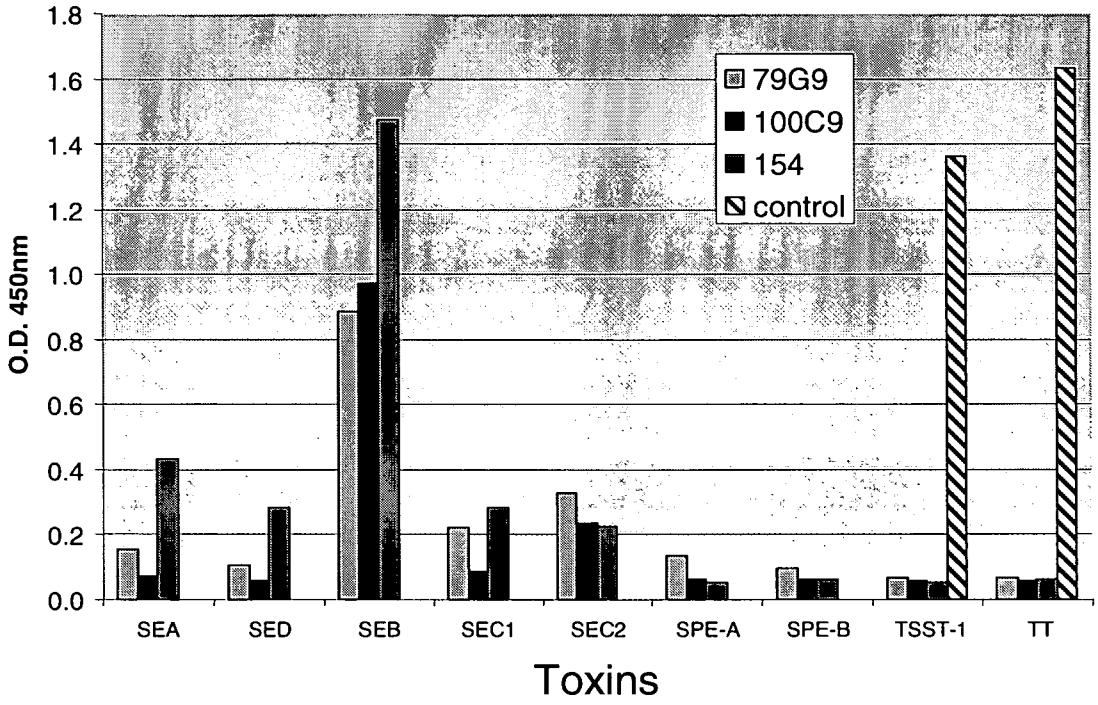
Figure 17A

Nucleotide	79G9+	79G9
51	A	C
55	A	T
56	G	C
63	G	A
70	T	G
71	T	A
73	C	G
710	A	G
1051	C	G
1137	T	G
1141	C	A
1290	C	T

Figure 17B

Amino Acid	79G9+	79G9
24	L	E
25	Q	E
237	K	R
351	L	V
379	D	E
381	L	M

Figure 18


1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
O.D. 450nm
79G9
100C9
154
control
SEA
SED
SEB
SEC1
SEC2
SPE-A
SPE-B
TSST-1
TT
Toxins