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(54) Title: USE OF ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES OR ANTIBODY FRAGMENTS TO TREAT OR PREVENT CHRONIC AND ACUTE FORMS OF DIARRHEA

(57) Abstract:

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USE OF ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES OR ANTIBODY FRAGMENTS TO TREAT OR PREVENT CHRONIC AND ACUTE FORMS OF DIARRHEA

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/496,873 (Atty. Docket No. 67858.770000) filed June 14, 2011, entitled "USE OF ANTI-CGRP ANTIBODIES AND ANTIBODY FRAGMENTS TO TREAT DIARRHEA IN SUBJECTS WITH DISEASES OR TREATMENTS THAT RESULT IN ELEVATED CGRP LEVELS" and U.S. Provisional Application No. 61/488,660 (Atty. Docket No. 67858.730300) filed May 20, 2011, entitled "ANTI-CGRP COMPOSITIONS AND USE THEREOF" each of which is hereby incorporated by reference in its entirety.

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 18, 2012, is named 67858o730304.txt and is 203,920 bytes in size.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] This invention pertains to the discovery that polypeptides that bind to CGRP or CGRP receptor and/or other polypeptides which inhibit the CGRP/CGRP receptor interaction such as anti-CGRP or anti-CGRP receptor antibodies and antibody fragments or fragments of CGRP or the CGRP receptor which inhibit the CGRP/CGRP receptor interaction may be used to treat or prevent diarrhea, especially diarrhea associated with conditions or treatments that result in increased levels of CGRP. Exemplary conditions and treatments involving increased CGRP are identified herein. The invention in particular relates to methods of inhibiting, preventing or treating diarrhea and/or maintaining electrolyte balance and fluid levels in the colon of a subject having a condition or treatment

associated with elevated CGRP levels that result in diarrhea and/or increased flux of electrolytes and fluids from the colon comprising administering an effective amount of an anti-CGRP antibody or anti-CGRP antibody fragment. Exemplary conditions include by way of example functional bowel disorder and inflammatory bowel diseases, bacterial or viral infections, and more specifically gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, diverticulosis, and diverticulitis, Crohn's disease, ileitis, collagenous colitis, lymphocytic colitis, ulcerative colitis, cancers or cancer treatments associated with increased CGRP and diarrhea such as chemotherapy, radiation, medullary thyroid carcinoma, and colorectal cancer.

[0004] In addition the present invention provides methods of screening polypeptides such as anti-CGRP or anti-CGRP receptor antibodies and fragments thereof (including Fab fragments) having binding specificity to human Calcitonin Gene Related Peptide (hereinafter "CGRP") as well as fragments of CGRP or a CGRP receptor in animal models to determine the in vivo effects thereof, especially their ability to antagonize the adverse side effects of CGRP and to treat conditions involving excess CGRP, especially CGRP associated conditions or treatments associated with diarrhea. The invention also pertains to methods of screening for diseases and disorders associated with increased CGRP, which are associated with diarrhea and specific therapeutic regimens for preventing or treating diseases and disorders that involve CGRP associated diarrhea by administering said antibodies or fragments thereof, alone or in association with other actives.

Description of Related Art

[0005] Calcitonin Gene Related Peptide (CGRP) is produced as a multifunctional neuropeptide of 37 amino acids in length. Two forms of CGRP, the CGRP-alpha and CGRP-beta forms, exist in humans and have similar activities. CGRP-alpha and CGRP-beta differ by three amino acids in humans, and are derived from different genes. The CGRP family of peptides includes amylin, adrenomedullin, and calcitonin, although each has distinct receptors and biological activities. Doods, H., *Curr. Op. Invest. Drugs*, 2(9):1261-68 (2001).

[0006] CGRP is released from numerous tissues such as trigeminal nerves, which when activated release neuropeptides within the meninges, mediating neurogenic inflammation that is characterized by vasodilation, vessel leakage, and mast-cell degradation. Durham, P.L., *New Eng. J. Med.*, 350 (11):1073-75 (2004). The biological effects of CGRP are mediated via the CGRP receptor (CGRP-R), which consists of a seven-transmembrane component, in conjunction with receptor-associated membrane protein (RAMP). CGRP-R further requires the activity of the receptor component protein (RCP), which is essential for an efficient coupling to adenylate cyclase through G proteins and the production of cAMP. Doods, H., *Curr. Op. Invest. Drugs*, 2(9):1261-68 (2001).

[0007] Migraines are neurovascular disorder affecting approximately 10% of the adult population in the U.S., and are typically accompanied by intense headaches. Approximately 20-30% of migraine sufferers experience aura, comprising focal neurological phenomena that precede and/or accompany the event. CGRP is believe to play a prominent role in the development of migraines. For example, plasma concentrations of CGRP were identified elevated in jugular venous blood during the headache phase of migraines, to the exclusion of other neuropeptides. Moreover, according to Arulmozhi *et al*, the following has been identified in migraine sufferers: (1) a strong correlation between plasma CGRP concentrations and migraines; (2) the infusion of CGRP produced a migraine-like headache; (3) baseline CGRP levels were elevated; and (4) changes in plasma CGRP levels during migraine attacks significantly correlated with headache intensity. Arulmozhi, D.K., *et al.*, Vas. Pharma., 43: 176-187 (2005). In addition, in the Journal of the International Association for the Study of Pain PII:S0304-3959(11)00313-7; doi:10.1016/j.pain.2011.04.033, published online 06 June 2011, Hou et al., reported that keratinocyte expression of calcitonin gene-related peptide β has implications for neuropathic and inflammatory pain mechanisms.

[0008] One effective treatment for migraines is the administration of triptans, which are a family of tryptamine-based drugs, including sumatriptan and rizatriptan. Members of this family have an affinity for multiple serotonin receptors, including 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F}. Members of this family of drugs selectively constrict cerebral vessels, but also cause vasoconstrictive effects on coronary vessels. Durham, P.L., *New Eng. J. Med.*, 350

(11):1073-75 (2004). There is a theoretical risk of coronary spasm in patients with established heart disease following administration, and cardiac events after taking triptans may rarely occur. Noted to be contraindicated for patients with coronary vascular disease.

[0009] Similarly, pain may often be addressed through the administration of certain narcotics or non-steroidal anti-inflammatory drugs (NSAIDs). However, the administration of these treatments may occur at the cost of certain negative consequences. NSAIDs have the potential to cause kidney failure, intestinal bleeding, and liver dysfunction. Narcotics have the potential to cause nausea, vomiting, imparied mental functioning, and addiction. Therefore, it is desirable to identify alternative treatments for pain in order to avoid certain of these negative consequences.

[00010] CGRP is believed to play a role in a multitude of diseases and disorders, including but not limited to migraines, headaches, and pain. Due to the perceived involvement of CGRP in these diseases and disorders, there remains a need in the art for compositions and methods useful for preventing or treating diseases and disorders associated with CGRP, while avoiding adverse side effects. There especially remains a need in the art for compositions or methods that reduce or inhibit diseases or disorders associated with CGRP, such as migraines, headaches, and pain.

[00011] Aside from the afore-mentioned conditions there is a need for treating other conditions or adverse side effects that are associated with increased CGRP. In this regard there has been some anecdotal evidence reported in the literature which suggest that increases in CGRP levels may have a role in some diseases associated with diarrhea. For example, it was reported by Rolston et al. in Digestive Diseases and Sciences , (April 1989) 34(4):612-6, "Intravenous calcitonin gene-related peptide stimulates net water secretion in rat colon in vivo" that exogenous calcitonin gene-related peptide has an effect on net flux of water and electrolytes in the rat small and large intestine. They report that in ligated intestinal loops, intravenous calcitonin gene-related peptide (CGRP) induced colonic fluid secretion but had no effect on the small intestine. Also they report using a single-pass perfusion technique, that they observed an immediate dose-dependent secretion of water by the rat colon upon intravenous administration of CGRP and also that the net secretion of sodium, potassium, and chloride were also raised. They suggest the implications of these

observations for the possible involvement of high circulation concentrations of CGRP in the watery diarrhea syndrome accompanying medullary thyroid carcinoma.

[00012] Further, it was reported by Keates et al., Gastroenterology 114:956-64(1998), "CGRP Upregulation in dorsal root ganglia and ilea mucosa during Clostridium difficile toxin A-induced enteritis in mice" that CGRP may play a role in toxin-A mediated diarrhea and that a CGRP antagonist substantially inhibited toxin-A mediated diarrhea and inflammation.

[00013] In addition, Picard et al. reported in International Journal of Radiation Biology , (2001), Vol. 77, No. 3, pp. 349-356 , "Presence of protective role of afferent nerves in early intestinal mucosal alterations induced by abdominal irradiation in rats" that CGRP levels increase after abdominal irradiation and particularly in radiation enteritis a condition characterized by diarrhea and other inflammatory reactions.

BRIEF SUMMARY OF THE INVENTION

[00014] Aside from being uncomfortable to the afflicted individual, diarrhea, especially if chronic or severe can be life threatening especially in geriatric patients and infants and young children as well as patients with diseases such as cancer and viral infection associated with chronic diarrhea that can substantially deplete fluid and electrolyte levels. There are 2 general types of diarrhea, acute and chronic.

[00015] Diarrhea is generally classified as a condition of having three or more loose or liquid bowel movements per day. It is a common cause of death in developing countries and the second most common cause of infant deaths worldwide. The loss of fluids through diarrhea can cause dehydration and electrolyte imbalances. In 2009 diarrhea was estimated to have caused 1.1 million deaths in people aged 5 and over and 1.5 million deaths in children under the age of 5. Oral rehydration solutions (ORS) with modest amounts of electrolytes and zinc tablets are the treatment of choice and have been estimated to have saved 50 million children in the past 25 years. ORS should be begun at early as possible. Vomiting does often occurs during the first hour or two of treatment with ORS, but this seldom prevents successful rehydration as most of the fluid is still absorbed. The World Health Organization (WHO) recommends that if a child vomits, to wait five or ten minutes and then start again more slowly.

[00016] Homemade solutions recommended by WHO include salted drinks (e.g. salted rice water or a salted yoghurt drink) and vegetable or chicken soup with salt. If available, supplemental potassium, as well as supplemental zinc, can be added to or given with this homemade solution. It is s also recommended that persons with diarrhea, if able, continue or resume eating as this speeds recovery of normal intestinal function and generally leads to diarrhea of shorter duration. Clean plain water can be one of several fluids given. There are commercial solutions such as Pedialyte, and relief agencies such as UNICEF widely distribute packets of salts and sugar.

[00017] Aside from the chronic and acute designations of diarrhea, this condition is also classified into different types which classifications are based on the cause and disease manifestations. One type is "secretory diarrhea". Secretory diarrhea means that there is an increase in the active secretion, or there is an inhibition of absorption. There is little to no structural damage. The most common cause of this type of diarrhea is a cholera toxin that stimulates the secretion of anions, especially chloride ions. In this type of diarrhea intestinal fluid secretion is isotonic with plasma even during fasting.[8] <> It continues even when there is no oral food intake.

[00018] A second type is "osmotic diarrhea". Osmotic diarrhea may occur when too much water is drawn into the bowels. If a person drinks solutions with excessive sugar or excessive salt, these can draw water from the body into the bowel and cause osmotic diarrhea. Also, osmotic diarrhea can also be the result of maldigestion (e.g., pancreatic disease or Coeliac disease), in which the nutrients are left in the lumen to pull in water. Or it can be caused by osmotic laxatives (which work to alleviate constipation by drawing water into the bowels). In healthy individuals, too much magnesium or vitamin C or undigested lactose can produce osmotic diarrhea and distention of the bowel. A person who has lactose intolerance can have difficulty absorbing lactose after an extraordinarily high intake of dairy products. In persons who have fructose malabsorption, excess fructose intake can also cause diarrhea. High-fructose foods that also have a high glucose content are more absorbable and less likely to cause diarrhea. Sugar alcohols such as sorbitol (often found in sugar-free foods) are difficult for the body to absorb and, in large amounts, may lead to osmotic diarrhea.

[00019] A third type of diarrhea is exudative diarrhea". Exudative diarrhea occurs with the presence of blood and pus in the stool. This occurs with inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, and infections such as E. coli or other forms of food poisoning.

[00020] A fourth type of diarrhea is "motility-related diarrhea". Motility-related diarrhea is caused by the rapid movement of food through the intestines (hypermotility). If the food moves too quickly through the gastrointestinal tract, there is not enough time for sufficient nutrients and water to be absorbed. This can be due to a vagotomy or diabetic neuropathy, or a complication of menstruation. Hyperthyroidism can produce hypermotility and lead to this type of diarrhea. Diarrhea can be treated with antimotility agents (such as loperamide). Hypermotility can be observed in people who have had portions of their bowel removed, allowing less total time for absorption of nutrients.

[00021] A fifth type of diarrhea is "is "inflammatory diarrhea is ". Inflammatory diarrhea occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids, and a decreased ability to absorb these lost fluids. Features of all three of the other types of diarrhea can be found in this type of diarrhea. It can be caused by bacterial infections, viral infections, parasitic infections, or autoimmune problems such as inflammatory bowel diseases. It can also be caused by tuberculosis, colon cancer, and enteritis.

[00022] A related condition to diarrhea is "dysentery". Generally, if there is blood visible in the stools, it is not diarrhea, but dysentery. The blood is trace of an invasion of bowel tissue. Dysentery is a symptom of, among others, Shigella, Entamoeba histolytica, and Salmonella.

[00023] Diarrhea is most commonly due to viral gastroenteritis with rotavirus, which accounts for 40% of cases in children under five. In travelers however bacterial infections predominate. Various toxins such as mushroom poisoning and drugs can also cause acute diarrhea.

[00024] As noted above, diarrhea may be classified as chronic or acute. "Chronic diarrhea can be the part of the presentations of a number of chronic medical conditions

affecting the intestine. Common causes include ulcerative colitis, Crohn's disease, microscopic colitis, celiac disease, irritable bowel syndrome and bile acid malabsorption.

[00025] There are many causes of infectious diarrhea, which include viruses, bacteria and parasites. Norovirus is the most common cause of viral diarrhea in adults, but rotavirus is the most common cause in children under five years old. Adenovirus types 40 and 41, and astroviruses cause a significant number of infections.

[00026] The bacterium Campylobacter is a common cause of bacterial diarrhea, but infections by Salmonellae, Shigellae and some strains of Escherichia coli (E.coli) are frequent. In the elderly, particularly those who have been treated with antibiotics for unrelated infections, a toxin produced by Clostridium difficile often causes severe diarrhea.

[00027] Some parasites may cause diarrhea such as the protozoan Giardia, which can cause chronic infections if these are not diagnosed and treated with drugs such as metronidazole, and Entamoeba histolytica.

[00028] Other causes of chronic diarrhea include:enzyme deficiencies or mucosal abnormality, as in food allergy and food intolerance, e.g. celiac disease (gluten intolerance), lactose intolerance (intolerance to milk sugar, common in non-Europeans), and fructose malabsorption, pernicious anemia, or impaired bowel function due to the inability to absorb vitamin B12, loss of pancreatic secretions, which may be due to cystic fibrosis or pancreatitis, structural defects, like short bowel syndrome (surgically removed bowel) and radiation fibrosis, such as usually follows cancer treatment and other drugs, including agents used in chemotherapy; and certain drugs, like orlistat, which inhibits the absorption of fat.

[00029] Ulcerative colitis is marked by chronic bloody diarrhea and inflammation mostly affects the distal colon near the rectum. Crohn's disease typically affects fairly well demarcated segments of bowel in the colon and often affects the end of the small bowel.

[00030] Another cause of diarrhea is irritable bowel syndrome (IBS) which usually presents with abdominal discomfort relieved by defecation and unusual stool (diarrhea or constipation) for at least 3 days a week over the previous 3 months. Symptoms of diarrhea-predominant IBS can be managed through a combination of dietary changes, soluble fiber supplements, and/or medications such as loperamide or codeine. About 30% of patients

with diarrhea-predominant IBS have bile acid malabsorption diagnosed with an abnormal SeHCAT test.

[00031] Other causes of diarrhea are chronic ethanol ingestion, ichemic bowel disease, mcroscopic colitis, ble salt malabsorption (primary bile acid diarrhea) where excessive bile acids in the colon produce a secretory diarrhea, hrmone-secreting tumors, (some hormones (e.g., serotonin) can cause diarrhea if excreted in excess (usually from a tumor)).

[00032] Medications such as loperamide (Imodium) and bismuth subsalicylate may be beneficial in treating some diarrhea conditions, however they may be contraindicated in certain situations.

[00033] While antibiotics are beneficial in certain types of acute diarrhea, they are usually not used except in specific situations. In fact, antibiotics can also cause diarrhea, and antibiotic-associated diarrhea is the most common adverse effect of treatment with general antibiotics.

[00034] Bismuth compounds such as in (Pepto-Bismol) may be used to treat some diarrhea conditions. Also, anti motility agents may be used to treat some diarrhea conditions. These include loperamide. Codeine is sometimes used in the treatment of diarrhea to slow down peristalsis and the passage of fecal material through the bowels. Also, bile acid sequestrants such as cholestyramine, colestipol and colesevelam can be effective in chronic diarrhea due to bile acid malabsorption.

[00035] Zinc supplementation may be used to treat some chronic diarrhea conditions. Probiotics may sometimes be used to reduce the duration of symptoms.

[00036] As mentioned, a second type of diarrhea is acute diarrhea. The most common cause of acute diarrhea is infection--viral, bacterial, and parasitic. Bacteria also can cause acute food poisoning. A third important cause of acute diarrhea is starting a new medication.

[00037] Other specific causes of acute diarrhea include viral gastroenteritis which is the most common cause of acute diarrhea worldwide. Viral gastroenteritis can occur in a sporadic form (in a single individual) or in an epidemic form (among groups of individuals). Sporadic diarrhea probably is caused by several different viruses and is believed to be spread by person-to-person contact. The most common cause of epidemic

diarrhea (for example, on cruise ships) is infection with a family of viruses known as caliciviruses of which the genus norovirus is the most common (for example, "Norwalk agent"). The caliciviruses are transmitted by food that is contaminated by sick food-handlers or by person-to-person contact.

[00038] Another cause of acute diarrhea is food poisoning caused by toxins produced by bacteria. The toxins cause abdominal pain (cramps) and vomiting and also cause the small intestine to secrete large amounts of water that leads to diarrhea. The symptoms of food poisoning usually last less than 24 hours. With some bacteria, the toxins are produced in the food before it is eaten, while with other bacteria, the toxins are produced in the intestine after the food is eaten.

[00039] Staphylococcus aureus is an example of a bacterium that produces toxins in food before it is eaten. Typically, food contaminated with Staphylococcus (such as salad, meat or sandwiches with mayonnaise) is left un-refrigerated at room temperature overnight. The Staphylococcal bacteria multiply in the food and produce toxins. Clostridium perfringens is an example of a bacterium that multiplies in food (usually canned food), and produces toxins in the small intestine after the contaminated food is eaten.

[00040] Another cause of acute diarrhea is traveler's diarrhea usually caused by pathogenic strains of E. coli bacteria. Occasionally, other bacteria or parasites can cause diarrhea in travelers (for example, Shigella, Giardia, Campylobacter). Diarrhea caused by these other organisms usually lasts longer than 3 days.

[00041] Yet another cause of acute diarrhea is bacterial enterocolitis which occurs when disease-causing bacteria usually invade the small intestines and colon and cause enterocolitis (inflammation of the small intestine and colon). Bacterial enterocolitis is characterized by signs of inflammation (blood or pus in the stool, fever) and abdominal pain and diarrhea. Campylobacter jejuni is the most common bacterium that causes acute enterocolitis in the U.S. Other bacteria that cause enterocolitis include Shigella, Salmonella, and EPEC. These bacteria usually are acquired by drinking contaminated water or eating contaminated foods such as vegetables, poultry, and dairy products.

[00042] Enterocolitis caused by the bacterium Clostridium difficile is often is caused by antibiotic treatment. Clostridium difficile is also the most common nosocomial infection

(infection acquired while in the hospital) to cause diarrhea. Unfortunately, infection also is increasing among individuals who have neither taken antibiotics or been in the hospital.

[00043] Another cause of acute diarrhea is E. coli O157:H7 which is a strain of E. coli that produces a toxin that causes hemorrhagic enterocolitis (enterocolitis with bleeding). There was a famous outbreak of hemorrhagic enterocolitis in the U.S. traced to contaminated ground beef in hamburgers (hence it is also called hamburger colitis). Approximately 5% of patients infected with E. coli O157:H7, particularly children, can develop hemolytic uremic syndrome (HUS), a syndrome that can lead to kidney failure . Some evidence suggests that prolonged use of anti-diarrhea agents or use of antibiotics may increase the chance of developing HUS.

[00044] Still anther cause of acute diarrhea is parasite infection, more common outside of the U. S. For example, infection with Giardia lamblia occurs among individuals who hike in the mountains or travel abroad and is transmitted by contaminated drinking water. Cryptosporidium is another diarrhea-producing parasite that is typically spread by contaminated water.

[00045] Yet anther cause of acute diarrhea is drug-induced diarrhea. The medications that most frequently cause diarrhea are antacids and nutritional supplements that contain magnesium. Other classes of medication that cause diarrhea include: nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy medications, antibiotics, medications to control irregular heartbeats (antiarrhythmics), and medications for high blood pressure. misoprostol (Cytotec), quinidine (Quinaglute, Quinidex), olsalazine (Dipentum), colchicine (Colchicine), metoclopramide (Reglan), and cisapride (Propulsid, Motilium).

[00046] Common causes of chronic diarrhea include irritable bowel syndrome. infectious diseases such as Giardia lamblia, AIDS infection, bacterial overgrowth of the small intestine, .post-infectious diarrhea wherein individuals following acute viral, bacterial or parasitic infections develop chronic diarrhea (also referred to as post-infectious IBS), inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis, and other diseases causing inflammation of the small intestine and/or colon, commonly cause chronic diarrhea, colon cancer, particularly in the distal part of the colon, can lead to thin stools. severe constipation, carbohydrate (sugar) malabsorption. such as lactase deficiency (also

known as lactose or milk intolerance), fat malabsorption pancreatitis or pancreatic cancer, diseases of the lining of the small intestine that prevent the absorption of digested fat such as celiac disease, endocrine diseases such as hyperthyroidism or an under-active pituitary or adrenal gland (Addison's disease) and laxative abuse.

[00047] Both acute and chronic diarrhea may involve adverse complications including dehydration resulting from an excessive loss of fluids and electrolytes from the body due to diarrhea. Dehydration is common among adult patients with acute diarrhea who have large amounts of stool, particularly when the intake of fluids is limited by lethargy or is associated with nausea and vomiting and is common in infants and young children who develop viral gastroenteritis or bacterial infection.

[00048] Moderate to severe dehydration may cause orthostatic hypotension with syncope (fainting upon standing due to a reduced volume of blood, which causes a drop in blood pressure upon standing), a diminished urine output, severe weakness, shock, kidney failure, confusion, acidosis (too much acid in the blood), and even coma.

[00049] Electrolytes (minerals) also are lost with water when diarrhea is prolonged or severe, and mineral or electrolyte deficiencies may occur. The most common deficiencies occur with sodium and potassium. Abnormalities of chloride and bicarbonate also may develop. Finally, there may be irritation of the anus due to the frequent passage of watery stool containing irritating substances.

[00050] Accordingly, an effective method of preventing or treating different forms of diarrhea such as are above-described, and in particular acute or chronic diarrhea would be beneficial.

[00051] Along those lines, the present invention provides methods and medicaments for treating or preventing CGRP associated diarrhea comprising the administration of at least one polypeptide that binds CGRP or the CGRP receptor and/or a polypeptide which inhibits the CGRP/CGRP receptor interaction. These polypeptides include anti-CGRP or anti-CGRP receptor antibodies and antibody fragments, and fragments or variants of CGRP or the CGRP receptor which inhibit the CGRP/CGRP receptor interaction. These therapies effectively treat or prevent diarrhea, especially diarrhea that occurs as a result of disease

conditions or treatments associated with increased levels of CGRP, e.g. increased levels in the gastrointestinal system and more particularly the colon.

[00052] The invention in particular relates to methods of inhibiting, preventing or treating diarrhea and/or maintaining electrolyte balance and fluid levels in the colon of a subject having a condition (e.g., gastrointestinal condition, cancer, viral or infectious disorder) or treatments associated resulting in elevated CGRP levels (such as radiation or chemotherapy) that result in diarrhea and/or increased flux of electrolytes and fluids from the colon comprising administering an effective amount of an anti-CGRP antibody or anti-CGRP antibody fragment. These conditions include by way of example functional bowel disorders and inflammatory bowel diseases, bacterial or viral induced diarrhea, radiation and chemotherapies and more specifically functional bowel disorders selected from the group consisting of gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, diverticulosis, and diverticulitis, inflammatory bowel diseases selected from the group consisting of Crohn's disease, ileitis, collagenous colitis, lymphocytic colitis, and ulcerative colitis, and cancers associated with diarrhea such as medullary thyroid carcinoma, and colorectal cancer.

[00053] The invention also relates to methods of screening antibodies and fragments thereof (including Fab fragments) having binding specificity to human Calcitonin Gene Related Peptide (hereinafter "CGRP") or the CGRP receptor or which inhibit the CGRP/CGRP receptor interaction in animal models to determine the in vivo effects thereof, especially their ability to antagonize the adverse side effects of CGRP and to treat or prevent diarrhea in conditions or treatments involving excess CGRP.

[00054] Further, the invention involves a method of assessing the potential in vivo efficacy of a candidate anti-CGRP antibody or antibody fragment or another polypeptide that inhibits the CGRP/CGRP receptor interaction for treating or preventing diarrhea comprising determining whether the antibody or other polypeptide inhibits diarrhea in a rodent administered exogenous CGRP compared to a rodent administered CGRP in the absence of the candidate CGRP antibody or antibody fragment or other polypeptide inhibitor.

[00055] Also, the invention involves a method of administering an anti-CGRP or anti-CGRP receptor antibody or antibody fragment or another polypeptide that inhibits the CGRP/CGRP receptor interaction to treat neurological and pain conditions characterized by increased CGRP levels which are associated with diarrhea.

[00056] Also the invention relates to medicaments for treating a condition associated with diarrhea selected from gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, diverticulosis, diverticulitis, Crohn's disease, ileitis, collagenous colitis, lymphocytic colitis, and ulcerative colitis, medullary thyroid carcinoma or a colorectal cancer.

[00057] Further the invention relates to methods of assessing based on results in a rodent CGRP animal model a suitable therapeutic dosage or dosage regimen of the candidate antibody or antibody fragment in humans for preventing or treating CGRP associated diarrhea.

[00058] Still further the invention relates to compositions for inhibiting, preventing or treating diarrhea and/or maintaining electrolyte balance and fluid levels in the colon of a subject having a condition associated with elevated CGRP levels that result in diarrhea and/or increased flux of electrolytes and fluids from the colon comprising an effective amount of an anti-CGRP or anti-CGRP receptor antibody or anti-CGRP or anti-CGRP receptor antibody fragment and optionally another active agent.

[00059] Related thereto the invention specifically relates to compositions for treating or preventing functional bowel disorders or an inflammatory bowel diseases, bacterial or viral induced diarrhea, cancer associated with diarrhea, such as medullary thyroid carcinoma or a colorectal cancer, and functional bowel disorders or inflammatory bowel diseases, including by way of example gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, diverticulosis, and diverticulitis or inflammatory bowel disease is selected from the group consisting of Crohn's disease, ileitis, collagenous colitis, lymphocytic colitis, and ulcerative colitis. wherein these therapies administer an effective amount of an anti-CGRP antibody or antibody fragment which is administered as a monotherapy or in combination with another active agent. .

[00060] In preferred embodiments the present invention is directed to therapeutic usage of specific antibodies and fragments thereof for treatment or prevention of diarrhea in diseases or treatments associated with in increased levels of CGRP, said antibodies or antibody fragments having binding specificity for CGRP, in particular antibodies having desired epitopic specificity, high affinity or avidity and/or functional properties. In other preferred embodiments this invention relates to assays and usage of the antibodies described herein, comprising the sequences of the V_H, V_L and CDR polypeptides described herein, and the polynucleotides encoding them. A preferred embodiment of the invention is directed to chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP and/or inhibiting the biological activities mediated by the binding of CGRP to the CGRP receptor ("CGRP-R").

[00061] In another preferred embodiment of the invention, the assays and therapies use full length antibodies and Fab fragments thereof for treatment or prevention of diarrhea in diseases or conditions resulting in increased levels of CGRP that inhibit the CGRP-alpha-, CGRP-beta-, and rat CGRP-driven production of cAMP. In a further preferred embodiment of the invention, full length and Fab fragments thereof are contemplated that reduce vasodilation in a recipient following administration.

[00062] In another embodiment of the invention, chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP or the CGRP receptor are useful in methods directed to reducing, treating, or preventing diarrhea in diseases or conditions resulting in increased levels of CGRP such as migraines (with or without aura), cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, weight loss, pain, hemiplagic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysomal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (such as for example associated with sinusitis), and allergy-induced headaches or migraines.

[00063] In another embodiment of the invention, chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP are useful in

methods directed to reducing, treating, or preventing diarrhea and visceral pain associated with gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, or pancreatitis.

[00064] In another embodiment of the invention these antibodies and humanized versions for treatment or prevention of diarrhea in diseases or conditions resulting in increased levels of CGRP may be derived from rabbit immune cells (B lymphocytes) and may be selected based on their homology (sequence identity) to human germ line sequences. These antibodies may require minimal or no sequence modifications, thereby facilitating retention of functional properties after humanization. A further embodiment of the invention is directed to fragments from anti-CGRP antibodies encompassing V_H, V_L and CDR polypeptides, e.g., derived from rabbit immune cells and the polynucleotides encoding the same, as well as the use of these antibody fragments and the polynucleotides encoding them in the creation of novel antibodies and polypeptide compositions capable of binding to CGRP and/or CGRP/CGRP-R complexes for treatment or prevention of diarrhea in diseases or conditions resulting in increased levels of CGRP.

[00065] The invention also contemplates conjugates of anti-CGRP antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties for treatment or prevention of diarrhea in diseases or conditions resulting in increased levels of CGRP. The invention also contemplates methods of making said chimeric or humanized anti-CGRP or anti-CGRP/CGRP-R complex antibodies and binding fragments thereof for treatment or prevention of diarrhea in diseases or conditions resulting in increased levels of CGRP. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv, scFv fragments, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR.

[00066] Embodiments of the invention pertain to the use of anti-CGRP antibodies and binding fragments thereof for the diagnosis, assessment and treatment of diseases and disorders associated with CGRP or aberrant expression thereof that result in diarrhea because of increased levels of CGRP. The invention also contemplates the use of fragments of anti-CGRP antibodies for the diagnosis, assessment and treatment of diseases

and disorders associated with CGRP or aberrant expression thereof such as diseases or conditions wherein increased levels of CGRP in the gut result in diarrhea. Other embodiments of the invention relate to the production of anti-CGRP antibodies or fragments thereof in recombinant host cells, for example mammalian cells such as CHO, NSO or HEK 293 cells, or yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[00067] Figure 1 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab1.

[00068] Figure 2 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab2.

[00069] Figure 3 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab3.

[00070] Figure 4 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab4.

[00071] Figure 5 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab5.

[00072] Figure 6 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab6.

[00073] Figure 7 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab7.

[00074] Figure 8 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab8.

[00075] Figure 9 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab9.

[00076] Figure 10 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab10.

[00077] Figure 11 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab11.

[00078] Figure 12 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab12.

[00079] Figure 13 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab13.

[00080] Figure 14 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab14.

[00081] Figure 15 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 infra for antibodies Ab1, Ab2, Ab3, and Ab4.

[00082] Figure 16 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 infra for antibodies Ab5, Ab6, Ab7, and Ab8.

[00083] Figure 17 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 infra for antibodies Ab9, Ab10, and Ab14.

[00084] Figure 18 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 infra for antibodies Ab11, Ab12, and Ab13.

[00085] Figure 19 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibodies Ab1, Ab2, and Ab4, obtained following the protocol in Example 1 infra.

[00086] Figure 20 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibody Ab3, obtained following the protocol in Example 1 infra.

[00087] Figure 21 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibodies Ab5 and Ab6, obtained following the protocol in Example 1 infra.

[00088] Figure 22 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibodies Ab7, Ab8, Ab9, and Ab10, obtained following the protocol in Example 1 infra.

[00089] Figure 23 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibodies Ab11, Ab12, and Ab13, obtained following the protocol in Example 1 infra.

[00090] Figure 24 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibody Ab14, obtained following the protocol in Example 1 infra.

[00091] Figure 25 demonstrates the inhibition of CGRP-beta-driven cAMP production by antibodies Ab1, Ab2, and Ab3, obtained following the protocol in Example 1 infra.

[00092] Figure 26 demonstrates the inhibition of CGRP-beta-driven cAMP production by antibodies Ab4, Ab5, and Ab6, obtained following the protocol in Example 1 infra.

[00093] Figure 27 demonstrates the inhibition of CGRP-beta-driven cAMP production by antibodies Ab7 and Ab8, obtained following the protocol in Example 1 infra.

[00094] Figure 28 demonstrates the inhibition of CGRP-beta-driven cAMP production by antibodies Ab9, Ab10, and Ab14, obtained following the protocol in Example 1 infra.

[00095] Figure 29 demonstrates the inhibition of CGRP-beta-driven cAMP production by antibodies Ab11, Ab12, and Ab13, obtained following the protocol in Example 1 infra.

[00096] Figure 30 demonstrates the inhibition of rat CGRP-driven cAMP production by antibodies Ab1, Ab2, Ab4, and Ab5, obtained following the protocol in Example 1 infra.

[00097] Figure 31 demonstrates the inhibition of rat CGRP -driven cAMP production by antibodies Ab3 and Ab6, obtained following the protocol in Example 1 infra.

[00098] Figure 32 demonstrates the inhibition of rat CGRP-driven cAMP production by antibodies Ab7 and Ab8, obtained following the protocol in Example 1 infra.

[00099] Figure 33 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab9, obtained following the protocol in Example 1 infra.

[000100] Figure 34 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab10, obtained following the protocol in Example 1 infra.

[000101] Figure 35 demonstrates the inhibition of rat CGRP-driven cAMP production by antibodies Ab11 and Ab12, obtained following the protocol in Example 1 infra.

[000102] Figure 36 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab13, obtained following the protocol in Example 1 infra.

[000103] Figure 37 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab14, obtained following the protocol in Example 1 infra.

[000104] Figure 38 demonstrates the inhibition of binding of radiolabeled CGRP to CGRP-R by antibodies Ab1-Ab13, obtained following the protocol in Example 6 infra.

[000105] Figure 39 demonstrates a reduction in vasodilation obtained by administering antibodies Ab3 and Ab6 following capsaicin administration in a rat model, relative to a control antibody, obtained following the protocol in Example 7 infra.

[000106] Figure 40 demonstrates a reduction in vasodilation obtained by administering antibody Ab6 at differing concentrations following capsaicin administration in a rat model, relative to a control antibody, obtained following the protocol in Example 7 infra.

[000107] Figure 41 contains the results of experiments wherein the effects of CGRP in transgenic Nestin/hRamp1 mice were evaluated. The data shows that rat CGRP-alpha administration induced diarrhea in Nestin/hRAMP1 tg mice and that the intra peritoneal injection of Ab3 (30mgs/kg, ~24 hrs. prior to CGRP challenge) inhibits intra cerebroventricular (ICV) injected, rat CGRP-alpha induced diarrhea in Nestin/hRAMP1 tg mice.

[000108] Figure 42 contains the results of experiments which show that the intra cerebroventricular (ICV) injection of human CGRP-alpha induces diarrhea in a dose dependent manner in C57BL/6J mice.

[000109] Figure 43 contains the results of experiments which show that intra peritoneal injection of Ab3 (30mgs/kg ip, ~24 hrs. prior to human CGRP-alpha challenge) inhibits ICV injected human CGRP-alpha induced diarrhea in C57/BL6J mice.

[000110] Figure 44 contains the results of experiments which show that Ab3 (30mgs/kg ip injection ~24 hrs. prior to human CGRP-alpha challenge) inhibits IP injected- human CGRP-alpha induced diarrhea in C57/BL6J mice.

[000111] FIG. 45 shows prevention of CGRP-induced diarrhea by Ab3 and Ab6 (both administered at 10 mg/kg). Negative control animals (treated with a control antibody and phosphate buffered saline, left bar) did not exhibit diarrhea, and 80% of positive control animals (treated with CGRP and a negative control antibody, filled bar) exhibited diarrhea. Administration of Ab3 (diagonal striped bar) and Ab6 (cross-hatched bar) reduced incidence of diarrhea to 40% and 60%, respectively.

[000112] FIG. 46 shows gross fecal weight resulting from CGRP-induced diarrhea for the experiment shown in FIG. 45. Gross fecal weight was greatly increased by administration of CGRP (second bar) compared to negative control animals (first bar). However, Ab3- and Ab6-treated animals exhibited greatly reduced gross fecal weight (third and fourth bars, respectively). Values shown are the average of all animals in each test group plus or minus standard error of mean (SEM).

[000113] FIG. 47 confirms prevention of CGRP-induced diarrhea by Ab3 and Ab6 in a further experiment (both antibodies administered at 30 mg/kg). Diarrhea was absent in negative control animals (treated with a control antibody and phosphate buffered saline, first bar) but observed in 80% of positive control animals (second bar, filled). Diarrhea incidence was reduced to 20% and 40%, respectively by Ab3 (third bar, diagonal stripes) and Ab6 (fourth bar, crosshatch).

[000114] FIG. 48 shows gross fecal weight resulting from CGRP-induced diarrhea for the experiment shown in FIG. 47. Gross fecal weight was greatly increased by administration of CGRP (second bar, filled) compared to negative control animals (first bar, unfilled). However, Ab6-treated animals exhibited greatly reduced gross fecal weight (fourth bar, checkered), and Ab3-treated animals (third bar, crosshatch) exhibited average gross fecal weight comparable to negative control animals (left bar, unfilled). Values shown are the average of all animals in each test group plus or minus standard error of mean (SEM).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

[000115] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the protein" includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise..

[000116] Calcitonin Gene Related Peptide (CGRP): As used herein, CGRP encompasses not only the following Homo sapiens CGRP-alpha and Homo sapiens CGRP-beta amino

acid sequences available from American Peptides (Sunnyvale CA) and Bachem (Torrance, CA):

[000117] CGRP-alpha: ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF-NH2 (SEQ ID NO: 281), wherein the N-terminal phenylalanine is amidated;

[000118] CGRP-beta: ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-NH2 (SEQ ID NO: 282), wherein the N-terminal phenylalanine is amidated; but also any membrane-bound forms of these CGRP amino acid sequences, as well as mutants (mutiens), splice variants, isoforms, orthologues, homologues and variants of this sequence. In particular CGRP herein encompasses rodent CGRPs and CGRP sequences of other mammals.

[000119] "CGRP receptor" herein includes all endogenous receptors that are specifically bound by CGRP, including human and rodent CGRP and other mammalian CGRP. As well CGRP receptor" includes mutants (mutiens), splice variants, isoforms, orthologues, homologues, fragments and variants of CGRP receptors that are specifically bound by CGRP. In particular CGRP receptor herein encompasses human, rat, murine and non-human primate CGRP receptors and CGRP receptor sequences of other mammals.

[000120] "CGRP/CGRP Receptor Inhibitor" herein refers to a molecule, preferably a polypeptide such as an antibody or antibody fragment that inhibits the interaction of CGRP and its receptor. Non-limiting examples thereof include antibodies and antibody fragments that specifically bind CGRP or the CGRP receptor and fragments of CGRP or the CGRP receptor.

[000121] "Diarrhea" refers to an increase in the frequency of bowel movements or a decrease in the form of stool (greater looseness of stool). Although changes in frequency of bowel movements and looseness of stools can vary independently of each other, changes often occur in both. Diarrhea needs to be distinguished from four other conditions. Although these conditions may accompany diarrhea, they often have different causes and different treatments than diarrhea. These other conditions are: incontinence of stool, which is the inability to control (delay) bowel movements until an appropriate time, for example, until one can get to the toilet , rectal urgency, which is a sudden urge to have a bowel movement that is so strong that if a toilet is not immediately available there will be

incontinence, incomplete evacuation, which is a sensation that another bowel movement is necessary soon after a bowel movement, yet there is difficulty passing further stool the second time and bowel movements immediately after eating a meal.

[000122] Diarrhea can be defined in absolute or relative terms based on either the frequency of bowel movements or the consistency (looseness) of stools.

[000123] Frequency of bowel movements. Absolute diarrhea is having more bowel movements than normal. Thus, since among healthy individuals the maximum number of daily bowel movements is approximately three, diarrhea can be defined as any number of stools greater than three. Relative diarrhea is having more bowel movements than usual. Thus, if an individual who usually has one bowel movement each day begins to have two bowel movements each day, then diarrhea is present-even though there are not more than three bowel movements a day, that is, there is not absolute diarrhea.

[000124] Consistency of stools. Absolute diarrhea is more difficult to define on the basis of the consistency of stool because the consistency of stool can vary considerably in healthy individuals depending on their diets. Thus, individuals who eat large amounts of vegetables will have looser stools than individuals who eat few vegetables. Stools that are liquid or watery are always abnormal and considered diarrheal. Relative diarrhea is easier to define based on the consistency of stool. Thus, an individual who develops looser stools than usual has diarrhea--even though the stools may be within the range of normal with respect to consistency.

[000125] Diarrhea generally is divided into two types, acute and chronic. Acute diarrhea lasts from a few days up to a week. Chronic diarrhea can be defined in several ways but almost always lasts more than three weeks. Acute and chronic diarrhea usually have different causes, require different diagnostic tests, and often involve different treatments.

[000126] "Treatment or prevention of CGRP-induced diarrhea" means that the treatment, e.g., administration of an anti-CGRP antibody or fragment effectively inhibits or treats diarrhea and/or maintains proper electrolyte and fluid levels in the colon of a subject in need thereof relative to an untreated subject.

[000127] "CGRP-induced diarrhea or CGRP-associated diarrhea" refers to a condition or treatment resulting in elevated CGRP levels, especially in the gastrointestinal system and

especially the colon that result in one or more of increased excretion of fluid from the colon, impaired electrolyte balance and one or more watery bowel movements (diarrhea).

[000128] "Treatments that result in CGRP-associated diarrhea" herein refer to any treatment for a disease condition, e.g., radiation, chemotherapy, drug therapy that result in increased CGRP levels that are associated with diarrhea.

[000129] 'CGRP associated disease or condition" is any disease or condition that is associated with increased CGRP levels relative to CGRP levels in normal individuals.

[000130] Mating competent yeast species: In the present invention this is intended to broadly encompass any diploid or tetraploid yeast which can be grown in culture. Such species of yeast may exist in a haploid, diploid, or other polyploid form. The cells of a given ploidy may, under appropriate conditions, proliferate for an indefinite number of generations in that form. Diploid cells can also sporulate to form haploid cells. Sequential mating can result in tetraploid strains through further mating or fusion of diploid strains. The present invention contemplates the use of haploid yeast, as well as diploid or other polyploid yeast cells produced, for example, by mating or spheroplast fusion.

[000131] In one embodiment of the invention, the mating competent yeast is a member of the Saccharomycetaceae family, which includes the genera Arxiozyma; Ascobotryozyma; Citeromyces; Debaryomyces; Dekkera; Eremothecium; Issatchenkia; Kazachstania; Kluyveromyces; Kodamaea; Lodderomyces; Pachysolen; Pichia; Saccharomyces; Saturnispora; Tetrapisispora; Torulaspora; Williopsis; and Zygosaccharomyces. Other types of yeast potentially useful in the invention include Yarrowia; Rhodosporidium; Candida; Hansenula; Filobasium; Sporidiobolus; Bullera; Leucosporidium and Filobasidella.

[000132] In a preferred embodiment of the invention, the mating competent yeast is a member of the genus Pichia. In a further preferred embodiment of the invention, the mating competent yeast of the genus Pichia is one of the following species: Pichia pastoris, Pichia methanolica, and Hansenula polymorpha (Pichia angusta). In a particularly preferred embodiment of the invention, the mating competent yeast of the genus Pichia is the species Pichia pastoris.

[000133] Haploid Yeast Cell: A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[000134] Polyploid Yeast Cell: A cell having more than one copy of its normal genomic (chromosomal) complement.

[000135] Diploid Yeast Cell: A cell having two copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells.

[000136] Tetraploid Yeast Cell: A cell having four copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells. Tetraploids may carry two, three, four or more different expression cassettes. Such tetraploids might be obtained in S. cerevisiae by selective mating homozygotic heterothallic a/a and alpha/alpha diploids and in Pichia by sequential mating of haploids to obtain auxotrophic diploids. For example, a [met his] haploid can be mated with [ade his] haploid to obtain diploid [his]; and a [met arg] haploid can be mated with [ade arg] haploid to obtain diploid [arg]; then the diploid [his] x diploid [arg] to obtain a tetraploid prototroph. It will be understood by those of skill in the art that reference to the benefits and uses of diploid cells may also apply to tetraploid cells.

[000137] Yeast Mating: The process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

[000138] Meiosis: The process by which a diploid yeast cell undergoes reductive division to form four haploid spore products. Each spore may then germinate and form a haploid vegetatively growing cell line.

[000139] Selectable Marker: A selectable marker is a gene or gene fragment that confers a growth phenotype (physical growth characteristic) on a cell receiving that gene as, for example through a transformation event. The selectable marker allows that cell to survive and grow in a selective growth medium under conditions in which cells that do not receive that selectable marker gene cannot grow. Selectable marker genes generally fall into several types, including positive selectable marker genes such as a gene that confers on a cell resistance to an antibiotic or other drug, temperature when two temperature sensitive ("ts") mutants are crossed or a ts mutant is transformed; negative selectable marker genes

such as a biosynthetic gene that confers on a cell the ability to grow in a medium without a specific nutrient needed by all cells that do not have that biosynthetic gene, or a mutagenized biosynthetic gene that confers on a cell inability to grow by cells that do not have the wild type gene; and the like. Suitable markers include but are not limited to: ZEO; G418; LYS3; MET1; MET3a; ADE1; ADE3; URA3; and the like.

[000140] Expression Vector: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, e.g. E. coli, and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Stearns, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

[000141] Expression vectors for use in the methods of the invention will further include yeast specific sequences, including a selectable auxotrophic or drug marker for identifying transformed yeast strains. A drug marker may further be used to amplify copy number of the vector in a yeast host cell.

[000142] The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in yeast cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, e.g. a signal sequence, and the like. A yeast origin of replication is optional, as expression vectors are often integrated into the yeast genome. In one embodiment of the invention, the polypeptide of

interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

[000143] Nucleic acids are "operably linked" when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (GatewayR Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[000144] Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, e.g., the presence or absence of a nutrient or a change in temperature.

[000145] The yeast promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the yeast genome; alternatively a selectable marker is used as the site for homologous recombination. Pichia transformation is described in Cregg et al. (1985) Mol. Cell. Biol. 5:3376-3385.

[000146] Examples of suitable promoters from Pichia include the AOX1 and promoter (Cregg et al. (1989) Mol. Cell. Biol. 9:1316-1323); ICL1 promoter (Menendez et al. (2003) Yeast 20(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham et al. (1997) Gene 186(1):37-44); and FLD1 promoter (Shen et al. (1998) Gene

216(1):93-102). The GAP promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

[000147] Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile , amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

[000148] The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, e.g. a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The S. cerevisiae alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from P. pastoris. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Other secretion signals of interest also include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, e.g., K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto et. al. Protein Eng 11(2) 75 (1998); and Kobayashi et. al. Therapeutic Apheresis 2(4) 257 (1998).

[000149] Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to

300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

[000150] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

[000151] Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

[000152] As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) Ann.Rev.Biochem. 58:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and E.coli –encoded recombination proteins. Recombination occurs between specific attachment (att) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda, in Lambda II, Weisberg, ed.(Cold Spring Harbor, NY:Cold Spring Harbor Press), pp. 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the att sites are hybrid

sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

[000153] Att sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing att B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites; and the like.

[000154] Folding, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. While non-covalent interactions are important in determining structure, usually the proteins of interest will have intra- and/or intermolecular covalent disulfide bonds formed by two cysteine residues. For naturally occurring proteins and polypeptides or derivatives and variants thereof, the proper folding is typically the arrangement that results in optimal biological activity, and can conveniently be monitored by assays for activity, e.g. ligand binding, enzymatic activity, etc.

[000155] In some instances, for example where the desired product is of synthetic origin, assays based on biological activity will be less meaningful. The proper folding of such molecules may be determined on the basis of physical properties, energetic considerations, modeling studies, and the like.

[000156] The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, i.e. foldases, chaperonins, etc. Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, etc. as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

[000157] For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the

haploid parental strains expresses a distinct folding enzyme, e.g. one strain may express BIP, and the other strain may express PDI or combinations thereof.

[000158] The terms "desired protein" or "desired antibody" are used interchangeably and refer generally to a parent antibody specific to a target, i.e., CGRP or a chimeric or humanized antibody or a binding portion thereof derived therefrom as described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies." A preferred source for producing antibodies useful as starting material according to the invention is rabbits. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies (such as scFvs), camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', F(ab')2 and the like. See Streltsov VA, et al., Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, Protein Sci. 2005 Nov;14(11):2901-9. Epub 2005 Sep 30; Greenberg AS, et al., A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks, Nature. 1995 Mar 9;374(6518):168-73; Nuttall SD, et al., Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries, Mol Immunol. 2001 Aug;38(4):313-26; Hamers-Casterman C, et al., Naturally occurring antibodies devoid of light chains, Nature. 1993 Jun 3;363(6428):446-8; Gill DS, et al., Biopharmaceutical drug discovery using novel protein scaffolds, Curr Opin Biotechnol. 2006 Dec;17(6):653-8. Epub 2006 Oct 19.

[000159] For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are

sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[000160] Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (e.g., a functional domain, catalytic amino acid residues, etc). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for in vitro mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

[000161] Chimeric antibodies according to the invention for treatment or prevention of diarrhea in diseases or conditions resulting in increased levels of CGRP may be made by recombinant means by combining the variable light and heavy chain regions (VL and VH), obtained from antibody producing cells of one species with the constant light and heavy

chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, e.g., in U.S. Patent No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions.

[000162] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. Although facially complex, the process is straightforward in practice. See, e.g., U.S. Patent No. 6,187,287, incorporated fully herein by reference.

[000163] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab', F(ab')2, or other fragments) may be synthesized. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest, e.g. diabodies, which comprise two distinct Fv specificities. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

[000164] Immunoglobulins and fragments thereof may be modified post-translationally, e.g. to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of additional effector molecules are provided infra.

[000165] A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (i.e., the polynucleotide sequence "encodes" the polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

[000166] A "heterologous" region or domain of a DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

[000167] A "coding sequence" is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

[000168] Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for

polynucleotides) and liposomes (for polypeptides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypepide encoded by said polynucleotide sequence.

[000169] "Amplification" of polynucleotide sequences is the in vitro production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, Bio/Technol., 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

[000170] The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., Ann. N.Y. Acad. Sci., 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 daltons (the "light chain"), and two identical heavy chains of molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the Fab region; the stem portion of the "Y" configuration is designated the FC region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

[000171] The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (i.e., the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ, μ, α, δ, and ε (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., Structural Concepts in Immunology and Immunochemistry, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., et al., Clinical Immunobiology, pp 1-18, W. B. Sanders (1980); Kohl, S., et al., Immunology, 48: 187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or λ (lambda). Each heavy chain class can be prepared with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

[000172] The expression "variable region" or "VR" refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain (VL) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[000173] The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (See Kabat, E. A. et al., Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat et al. ("Sequences of Proteins of Immunological Interest," Kabat E., et al., US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-

dimensional structures of antibodies (Chothia and Lesk, J Mol. Biol. 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction (Kashmiri, S., Methods, 36:25-34 (2005)).

[000174] The expressions "framework region" or "FR" refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (See Kabat, E. A. et al., Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

ANTI-CGRP ANTIBODIES AND BINDING FRAGMENTS THEREOF HAVING BINDING ACTIVITY FOR CGRP

Antibody Ab1

[000175] The present invention broadly contemplates the use of any anti-CGRP antibody or antibody fragment for the treatment or prevention of CGRP-associated diarrhea in any disease or condition resulting in increased levels of CGRP that are involved in diarrhea, and/or increased fluid or electrolyte excretion from the colon. Conditions and treatments resulting in increased CGRP which is associated with diarrhea are identified in this application.

[000176] In one preferred embodiment, the invention includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQTASPVSAAVGSTVTINCQASQSVYDNNYLAWYQQKPGQPPKQLIYSTSTL ASGVSSRFKGSGSGTQFTLTISDLECADAATYYCLGSYDCSSGDCFVFGGGTEVVV KR (SEQ ID NO: 1).

[000177] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQTASPVSAAVGSTVTINCQASQSVYDNNYLAWYQQKPGQPPKQLIYSTSTL ASGVSSRFKGSGSGTQFTLTISDLECADAATYYCLGSYDCSSGDCFVFGGGTEVVV KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 2).

[000178] The invention further includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGTPLTLTCTVSGLDLSSYYMQWVRQAPGKGLEWIGVIGINDNT YYASWAKGRFTISRASSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 3).

[000179] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGTPLTLTCTVSGLDLSSYYMQWVRQAPGKGLEWIGVIGINDNT YYASWAKGRFTISRASSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 4).

[000180] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 5; SEQ ID NO: 6; and SEQ ID NO: 7 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence

of SEQ ID NO: 1 or the light chain sequence of SEQ ID NO: 2, and/or one or more of the polypeptide sequences of SEQ ID NO: 8; SEQ ID NO: 9; and SEQ ID NO: 10 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or the heavy chain sequence of SEQ ID NO: 4, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000181] The invention also contemplates fragments of the antibody for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1 or SEQ ID NO: 2. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

[000182] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 5; SEQ ID NO: 6; and SEQ ID NO: 7 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 1 or the light chain sequence of SEQ ID NO: 2.

[000183] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 8; SEQ ID NO: 9; and SEQ ID NO: 10 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 3 or the heavy chain sequence of SEQ ID NO: 4.

[000184] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, fragments of the antibodies

having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 1; the variable heavy chain region of SEQ ID NO: 3; the complementarity-determining regions (SEQ ID NO: 5; SEQ ID NO: 6; and SEQ ID NO: 7) of the variable light chain region of SEQ ID NO: 1; and the complementarity-determining regions (SEQ ID NO: 8; SEQ ID NO: 9; and SEQ ID NO: 10) of the variable heavy chain region of SEQ ID NO: 3.

[000185] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab1, comprising, or alternatively consisting of, SEQ ID NO: 2 and SEQ ID NO: 4, and having at least one of the biological activities set forth herein.

[000186] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab1, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 1 and the variable heavy chain sequence of SEQ ID NO: 3. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 1 and/or SEQ ID NO: 3 in said Fab while retaining binding specificity for CGRP.

[000187] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab1. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab1 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab2

[000188] In one embodiment, the invention includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSSGDCFVFGGGTKVEIK R (SEQ ID NO: 11).

[000189] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSSGDCFVFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 12).

[000190] The invention further includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGIN DNTYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT VSS (SEQ ID NO: 13).

[000191] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGIN DNTYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK

TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 14).

[000192] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 11 or the light chain sequence of SEQ ID NO: 12, and/or one or more of the polypeptide sequences of SEQ ID NO: 18; SEQ ID NO: 19; and SEQ ID NO: 20 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 13 or the heavy chain sequence of SEQ ID NO: 14, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000193] The invention also contemplates fragments of the antibody for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 11 or SEQ ID NO: 12. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 13 or SEQ ID NO: 14.

[000194] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 11 or the light chain sequence of SEQ ID NO: 12.

[000195] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID

NO: 18; SEQ ID NO: 19; and SEQ ID NO: 20 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 13 or the heavy chain sequence of SEQ ID NO: 14.

[000196] The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 11; the variable heavy chain region of SEQ ID NO: 13; the complementarity-determining regions (SEQ ID NO: 15; SEQ ID NO: 16; and SEQ ID NO: 17) of the variable light chain region of SEQ ID NO: 11; and the complementarity-determining regions (SEQ ID NO: 18; SEQ ID NO: 19; and SEQ ID NO: 20) of the variable heavy chain region of SEQ ID NO: 13.

[000197] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab2, comprising, or alternatively consisting of, SEQ ID NO: 12 and SEQ ID NO: 14, and having at least one of the biological activities set forth herein.

[000198] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab2, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 11 and the variable heavy chain sequence of SEQ ID NO: 13. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 11 and/or SEQ ID NO: 13 in said Fab while retaining binding specificity for CGRP.

[000199] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab2. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab2 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO

or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab3

[000200] In one embodiment, the invention includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSSGDCFVFGGGTKVEIK R (SEQ ID NO: 21).

[000201] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSSGDCFVFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 22).

[000202] The invention further includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGIN DNTYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT VSS (SEQ ID NO: 23).

[000203] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGIN DNTYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT

VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 24).

[000204] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 25; SEQ ID NO: 26; and SEQ ID NO: 27 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21 or the light chain sequence of SEQ ID NO: 22, and/or one or more of the polypeptide sequences of SEQ ID NO: 28; SEQ ID NO: 29; and SEQ ID NO: 30 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 23 or the heavy chain sequence of SEQ ID NO: 24, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000205] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 21 or SEQ ID NO: 22. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 23 or SEQ ID NO: 24.

[000206] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 25; SEQ ID NO: 26; and SEQ ID NO: 27 which

correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 21 or the light chain sequence of SEQ ID NO: 22.

[000207] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 28; SEQ ID NO: 29; and SEQ ID NO: 30 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 23 or the heavy chain sequence of SEQ ID NO: 24.

[000208] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 21; the variable heavy chain region of SEQ ID NO: 23; the complementarity-determining regions (SEQ ID NO: 25; SEQ ID NO: 26; and SEQ ID NO: 27) of the variable light chain region of SEQ ID NO: 21; and the complementarity-determining regions (SEQ ID NO: 28; SEQ ID NO: 29; and SEQ ID NO: 30) of the variable heavy chain region of SEQ ID NO: 23.

[000209] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab3, comprising, or alternatively consisting of, SEQ ID NO: 22 and SEQ ID NO: 24, and having at least one of the biological activities set forth herein.

[000210] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab3, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 21 and the variable heavy chain sequence of SEQ ID NO: 23. This embodiment of the invention further contemplates additions,

deletions, and variants of SEQ ID NO: 21 and/or SEQ ID NO: 23 in said Fab while retaining binding specificity for CGRP.

[000211] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab3. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab3 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab4

[000212] In one embodiment, the invention includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQTPSPVSAAVGSTVTINCQASQSVYHNTYLAWYQQKPGQPPKQLIYDASTL ASGVPSRFSGSGSGTQFTLTISGVQCNDAAAYYCLGSYDCTNGDCFVFGGGTEVV VKR (SEQ ID NO: 31).

[000213] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQTPSPVSAAVGSTVTINCQASQSVYHNTYLAWYQQKPGQPPKQLIYDASTL ASGVPSRFSGSGSGTQFTLTISGVQCNDAAAYYCLGSYDCTNGDCFVFGGGTEVV VKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 32).

[000214] The invention further includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGTPLTLTCSVSGIDLSGYYMNWVRQAPGKGLEWIGVIGINGAT

YYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 33).

[000215] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGTPLTLTCSVSGIDLSGYYMNWVRQAPGKGLEWIGVIGINGAT YYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 34).

[000216] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 35; SEQ ID NO: 36; and SEQ ID NO: 37 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 31 or the light chain sequence of SEQ ID NO: 32, and/or one or more of the polypeptide sequences of SEQ ID NO: 38; SEQ ID NO: 39; and SEQ ID NO: 40 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 33 or the heavy chain sequence of SEQ ID NO: 34, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000217] The invention also contemplates fragments of the antibody for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or

alternatively consist of, the polypeptide sequence of SEQ ID NO: 31 or SEQ ID NO: 32. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 33 or SEQ ID NO: 34.

[000218] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 35; SEQ ID NO: 36; and SEQ ID NO: 37 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 31 or the light chain sequence of SEQ ID NO: 32.

[000219] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 38; SEQ ID NO: 39; and SEQ ID NO: 40 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 33 or the heavy chain sequence of SEQ ID NO: 34.

[000220] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 31; the variable heavy chain region of SEQ ID NO: 33; the complementarity-determining regions (SEQ ID NO: 35; SEQ ID NO: 36; and SEQ ID NO: 37) of the variable light chain region of SEQ ID NO: 31; and the complementarity-determining regions (SEQ ID NO: 38; SEQ ID NO: 39; and SEQ ID NO: 40) of the variable heavy chain region of SEQ ID NO: 33.

[000221] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab4, comprising, or alternatively consisting of, SEQ ID NO: 32 and SEQ ID NO: 34, and having at least one of the biological activities set forth herein.

[000222] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab4, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 31 and the variable heavy chain sequence of SEQ ID NO: 33. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 31 and/or SEQ ID NO: 33 in said Fab while retaining binding specificity for CGRP.

[000223] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab4. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab4 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[000224] Antibody Ab5

[000225] In one embodiment, the invention includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIK R (SEQ ID NO: 41).

[000226] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES

VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 42).

[000227] The invention further includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGIN GATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT VSS (SEQ ID NO: 43).

[000228] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGIN GATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 44).

[000229] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 45; SEQ ID NO: 46; and SEQ ID NO: 47 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 41 or the light chain sequence of SEQ ID NO: 42, and/or one or more of the polypeptide sequences of SEQ ID NO: 48; SEQ ID NO: 49; and SEQ ID NO: 50 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 43 or the heavy chain sequence of SEQ ID NO: 44, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments

thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000230] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 41 or SEQ ID NO: 42. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 43 or SEQ ID NO: 44.

[000231] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 45; SEQ ID NO: 46; and SEQ ID NO: 47 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 41 or the light chain sequence of SEQ ID NO: 42.

[000232] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 48; SEQ ID NO: 49; and SEQ ID NO: 50 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 43 or the heavy chain sequence of SEQ ID NO: 44.

[000233] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 41; the variable heavy chain region of SEQ ID NO: 43; the complementarity-determining regions (SEQ ID NO: 45; SEQ ID NO: 46; and SEQ ID NO: 47) of the variable light chain region of SEQ ID NO: 41; and the complementarity-

determining regions (SEQ ID NO: 48; SEQ ID NO: 49; and SEQ ID NO: 50) of the variable heavy chain region of SEQ ID NO: 43.

[000234] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab5, comprising, or alternatively consisting of, SEQ ID NO: 42 and SEQ ID NO: 44, and having at least one of the biological activities set forth herein.

[000235] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab5, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 41 and the variable heavy chain sequence of SEQ ID NO: 43. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 41 and/or SEQ ID NO: 43 in said Fab while retaining binding specificity for CGRP.

[000236] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab5. In another embodiment of the invention, anti-CGRP antibodies such as Ab5 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[000237] Antibody Ab6

[000238] In one embodiment, the invention includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIK R (SEQ ID NO: 51).

[000239] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and

possessing a light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 52).

[000240] The invention further includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGIN GATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT VSS (SEQ ID NO: 53).

[000241] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGIN GATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 54).

[000242] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 51 or the light chain sequence of SEQ ID NO: 52, and/or one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and

SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 53 or the heavy chain sequence of SEQ ID NO: 54, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000243] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 51 or SEQ ID NO: 52. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 53 or SEQ ID NO: 54.

[000244] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 51 or the light chain sequence of SEQ ID NO: 52.

[000245] In a further embodiment of the invention, fragments of the antibody for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 53 or the heavy chain sequence of SEQ ID NO: 54.

[000246] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one, two, three or more, including

all of the following antibody fragments: the variable light chain region of SEQ ID NO: 51; the variable heavy chain region of SEQ ID NO: 53; the complementarity-determining regions (SEQ ID NO: 55; SEQ ID NO: 56; and SEQ ID NO: 57) of the variable light chain region of SEQ ID NO: 51; and the complementarity-determining regions (SEQ ID NO: 58; SEQ ID NO: 59; and SEQ ID NO: 60) of the variable heavy chain region of SEQ ID NO: 53.

[000247] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab6, comprising, or alternatively consisting of, SEQ ID NO: 52 and SEQ ID NO: 54, and having at least one of the biological activities set forth herein.

[000248] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 51 and the variable heavy chain sequence of SEQ ID NO: 53. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 51 and/or SEQ ID NO: 53 in said Fab while retaining binding specificity for CGRP.

[000249] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab6. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab6 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab7

[000250] In one embodiment, the invention includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and

possessing a variable light chain sequence comprising the sequence set forth below: QVLTQTASPVSAAVGSTVTINCQASQSVYNYNYLAWYQQKPGQPPKQLIYSTSTL ASGVSSRFKGSGSGTQFTLTISDVQCDDAATYYCLGSYDCSTGDCFVFGGGTEVV VKR (SEQ ID NO: 61).

[000251] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQTASPVSAAVGSTVTINCQASQSVYNYNYLAWYQQKPGQPPKQLIYSTSTL ASGVSSRFKGSGSGTQFTLTISDVQCDDAATYYCLGSYDCSTGDCFVFGGGTEVV VKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 62).

[000252] The invention further includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: QEQLKESGGRLVTPGTSLTLTCTVSGIDLSNHYMQWVRQAPGKGLEWIGVVGING RTYYASWAKGRFTISRTSSTTVDLKMTRLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 63).

[000253] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: QEQLKESGGRLVTPGTSLTLTCTVSGIDLSNHYMQWVRQAPGKGLEWIGVVGING RTYYASWAKGRFTISRTSSTTVDLKMTRLTTEDTATYFCARGDIWGPGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 64).

[000254] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 65; SEQ ID NO: 66; and SEQ ID NO: 67 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 61 or the light chain sequence of SEQ ID NO: 62, and/or one or more of the polypeptide sequences of SEQ ID NO: 68; SEQ ID NO: 69; and SEQ ID NO: 70 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 63 or the heavy chain sequence of SEQ ID NO: 64, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000255] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 61 or SEQ ID NO: 62. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 63 or SEQ ID NO: 64.

[000256] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 65; SEQ ID NO: 66; and SEQ ID NO: 67 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 61 or the light chain sequence of SEQ ID NO: 62.

[000257] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 68; SEQ ID NO: 69; and SEQ ID NO: 70 which correspond to the complementarity-

determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 63 or the heavy chain sequence of SEQ ID NO: 64.

[000258] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 61; the variable heavy chain region of SEQ ID NO: 63; the complementarity-determining regions (SEQ ID NO: 65; SEQ ID NO: 66; and SEQ ID NO: 67) of the variable light chain region of SEQ ID NO: 61; and the complementarity-determining regions (SEQ ID NO: 68; SEQ ID NO: 69; and SEQ ID NO: 70) of the variable heavy chain region of SEQ ID NO: 63.

[000259] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab7, comprising, or alternatively consisting of, SEQ ID NO: 62 and SEQ ID NO: 64, and having at least one of the biological activities set forth herein.

[000260] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab7, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 61 and the variable heavy chain sequence of SEQ ID NO: 63. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 61 and/or SEQ ID NO: 63 in said Fab while retaining binding specificity for CGRP.

[000261] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab7. In another embodiment of the invention, anti-CGRP antibodies such as Ab7 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial

systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab8

[000262] In one embodiment, the invention includes chimeric or humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below:
QVLTQSPSSLSASVGDRVTINCQASQSVYNYNYLAWYQQKPGKVPKQLIYSTSTL
ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSTGDCFVFGGGTKVEIK
R (SEQ ID NO: 71).

[000263] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below:
QVLTQSPSSLSASVGDRVTINCQASQSVYNYNYLAWYQQKPGKVPKQLIYSTSTL
ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSTGDCFVFGGGTKVEIK
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES
VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
(SEQ ID NO: 72).

[000264] The invention further includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSNHYMQWVRQAPGKGLEWVGVVGIN
GRTYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT
VSS (SEQ ID NO: 73).

[000265] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below:
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSNHYMQWVRQAPGKGLEWVGVVGIN
GRTYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT

VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 74).

[000266] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 75; SEQ ID NO: 76; and SEQ ID NO: 77 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 71 or the light chain sequence of SEQ ID NO: 72, and/or one or more of the polypeptide sequences of SEQ ID NO: 78; SEQ ID NO: 79; and SEQ ID NO: 80 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 73 or the heavy chain sequence of SEQ ID NO: 74, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000267] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 71 or SEQ ID NO: 72. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 73 or SEQ ID NO: 74.

[000268] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 75; SEQ ID NO: 76; and SEQ ID NO: 77 which correspond to the complementarity-

determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 71 or the light chain sequence of SEQ ID NO: 72.

[000269] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 78; SEQ ID NO: 79; and SEQ ID NO: 80 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 73 or the heavy chain sequence of SEQ ID NO: 74.

[000270] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 71; the variable heavy chain region of SEQ ID NO: 73; the complementarity-determining regions (SEQ ID NO: 75; SEQ ID NO: 76; and SEQ ID NO: 77) of the variable light chain region of SEQ ID NO: 71; and the complementarity-determining regions (SEQ ID NO: 78; SEQ ID NO: 79; and SEQ ID NO: 80) of the variable heavy chain region of SEQ ID NO: 73.

[000271] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab8, comprising, or alternatively consisting of, SEQ ID NO: 72 and SEQ ID NO: 74, and having at least one of the biological activities set forth herein.

[000272] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab8, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 71 and the variable heavy chain sequence of SEQ ID NO: 73. This embodiment of the invention further contemplates additions,

deletions, and variants of SEQ ID NO: 71 and/or SEQ ID NO: 73 in said Fab while retaining binding specificity for CGRP.

[000273] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab8. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab8 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab9

[000274] In one embodiment, the invention includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQTPSPVSAAVGSTVTINCQASQNVYNNNYLAWYQQKPGQPPKQLIYSTSTL ASGVSSRFRGSGSGTQFTLTISDVQCDDAATYYCLGSYDCSRGDCFVFGGGTEVV VKR (SEQ ID NO: 81).

[000275] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQTPSPVSAAVGSTVTINCQASQNVYNNNYLAWYQQKPGQPPKQLIYSTSTL ASGVSSRFRGSGSGTQFTLTISDVQCDDAATYYCLGSYDCSRGDCFVFGGGTEVV VKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 82).

[000276] The invention further includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGTPLTLTCTVSGIGLSSYYMQWVRQSPGRGLEWIGVIGSDGKT

YYATWAKGRFTISKTSSTTVDLRMASLTTEDTATYFCTRGDIWGPGTLVTVSS (SEQ ID NO: 83).

[000277] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGTPLTLTCTVSGIGLSSYYMQWVRQSPGRGLEWIGVIGSDGKT YYATWAKGRFTISKTSSTTVDLRMASLTTEDTATYFCTRGDIWGPGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 84).

[000278] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 85; SEQ ID NO: 86; and SEQ ID NO: 87 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 81 or the light chain sequence of SEQ ID NO: 82, and/or one or more of the polypeptide sequences of SEQ ID NO: 88; SEQ ID NO: 89; and SEQ ID NO: 90 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 83 or the heavy chain sequence of SEQ ID NO: 84, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000279] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one

embodiment of the invention, antibody fragments of the invention for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 81 or SEQ ID NO: 82. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 83 or SEQ ID NO: 84.

[000280] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 85; SEQ ID NO: 86; and SEQ ID NO: 87 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 81 or the light chain sequence of SEQ ID NO: 82.

[000281] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 88; SEQ ID NO: 89; and SEQ ID NO: 90 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 83 or the heavy chain sequence of SEQ ID NO: 84.

[000282] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 81; the variable heavy chain region of SEQ ID NO: 83; the complementarity-determining regions (SEQ ID NO: 85; SEQ ID NO: 86; and SEQ ID NO: 87) of the variable light chain region of SEQ ID NO: 81; and the complementarity-determining regions (SEQ ID NO: 88; SEQ ID NO: 89; and SEQ ID NO: 90) of the variable heavy chain region of SEQ ID NO: 83.

[000283] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab9, comprising,

or alternatively consisting of, SEQ ID NO: 82 and SEQ ID NO: 84, and having at least one of the biological activities set forth herein.

[000284] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab9, the Fab fragment for the treatment or prevention of CGRP-associated diarrhea includes the variable light chain sequence of SEQ ID NO: 81 and the variable heavy chain sequence of SEQ ID NO: 83. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 81 and/or SEQ ID NO: 83 in said Fab while retaining binding specificity for CGRP.

[000285] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab9. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab9 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab10

[000286] In one embodiment, the invention includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSRGDCFVFGGGTKVEIK R (SEQ ID NO: 91).

[000287] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTL

ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSRGDCFVFGGGTKVEIK
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES
VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
(SEQ ID NO: 92).

[000288] The invention further includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSD
GKTYYATWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCTRGDIWGQGTLVT
VSS (SEQ ID NO: 93).

[000289] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSD
GKTYYATWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCTRGDIWGQGTLVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 94).

[000290] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 91 or the light chain sequence of SEQ ID NO: 92, and/or one or more of the polypeptide sequences of SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 93 or the

heavy chain sequence of SEQ ID NO: 94, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000291] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 91 or SEQ ID NO: 92. In another embodiment of the invention, antibody fragments of the invention for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 93 or SEQ ID NO: 94.

[000292] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 91 or the light chain sequence of SEQ ID NO: 92.

[000293] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 93 or the heavy chain sequence of SEQ ID NO: 94.

[000294] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 91; the variable heavy chain region of SEQ ID NO: 93; the

complementarity-determining regions (SEQ ID NO: 95; SEQ ID NO: 96; and SEQ ID NO: 97) of the variable light chain region of SEQ ID NO: 91; and the complementarity-determining regions (SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID NO: 100) of the variable heavy chain region of SEQ ID NO: 93.

[000295] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab10, comprising, or alternatively consisting of, SEQ ID NO: 92 and SEQ ID NO: 94, and having at least one of the biological activities set forth herein.

[000296] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab10, the Fab fragment for the treatment or prevention of CGRP-associated diarrhea includes the variable light chain sequence of SEQ ID NO: 91 and the variable heavy chain sequence of SEQ ID NO: 93. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 91 and/or SEQ ID NO: 93 in said Fab while retaining binding specificity for CGRP.

[000297] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab10. In another embodiment of the invention, anti-CGRP antibodies such as Ab10 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab11

[000298] In one embodiment, the invention includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQTASPVSPAVGSTVTINCRASQSVYYNNYLAWYQQKPGQPPKQLIYSTSTLA

SGVSSRFKGSGSGTQFTLTISDVQCDDAATYYCLGSYDCSNGDCFVFGGGTEVVV KR (SEQ ID NO: 101).

[000299] The invention also includes chimeric antibodies having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: QVLTQTASPVSPAVGSTVTINCRASQSVYYNNYLAWYQQKPGQPPKQLIYSTSTLA SGVSSRFKGSGSGTQFTLTISDVQCDDAATYYCLGSYDCSNGDCFVFGGGTEVVV KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 102).

[000300] The invention further includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGGSLTLTCTVSGIDVTNYYMQWVRQAPGKGLEWIGVIGVNGK RYYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 103).

[000301] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: QSLEESGGRLVTPGGSLTLTCTVSGIDVTNYYMQWVRQAPGKGLEWIGVIGVNGK RYYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 104).

[000302] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 105; SEQ ID NO: 106; and SEQ ID NO: 107 which correspond to the

complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101 or the light chain sequence of SEQ ID NO: 102, and/or one or more of the polypeptide sequences of SEQ ID NO: 108; SEQ ID NO: 109; and SEQ ID NO: 110 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 103 or the heavy chain sequence of SEQ ID NO: 104, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000303] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 101 or SEQ ID NO: 102. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 103 or SEQ ID NO: 104.

[000304] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 105; SEQ ID NO: 106; and SEQ ID NO: 107 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 101 or the light chain sequence of SEQ ID NO: 102.

[000305] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 108; SEQ ID NO: 109; and SEQ ID NO: 110 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 103 or the heavy chain sequence of SEQ ID NO: 104.

[000306] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 101; the variable heavy chain region of SEQ ID NO: 103; the complementarity-determining regions (SEQ ID NO: 105; SEQ ID NO: 106; and SEQ ID NO: 107) of the variable light chain region of SEQ ID NO: 101; and the complementarity-determining regions (SEQ ID NO: 108; SEQ ID NO: 109; and SEQ ID NO: 110) of the variable heavy chain region of SEQ ID NO: 103.

[000307] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab11, comprising, or alternatively consisting of, SEQ ID NO: 102 and SEQ ID NO: 104, and having at least one of the biological activities set forth herein.

[000308] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab11, the Fab fragment for the treatment or prevention of CGRP-associated diarrhea includes the variable light chain sequence of SEQ ID NO: 101 and the variable heavy chain sequence of SEQ ID NO: 103. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 101 and/or SEQ ID NO: 103 in said Fab while retaining binding specificity for CGRP.

[000309] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab11. In another embodiment of the invention, anti-CGRP antibodies such as Ab11 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial

systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab12

[000310] In one embodiment, the invention includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below:
QVLTQSPSSLSASVGDRVTINCRASQSVYYNNYLAWYQQKPGKVPKQLIYSTSTL
ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSNGDCFVFGGGTKVEIK
R (SEQ ID NO: 111).

[000311] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below:
QVLTQSPSSLSASVGDRVTINCRASQSVYYNNYLAWYQQKPGKVPKQLIYSTSTL
ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSNGDCFVFGGGTKVEIK
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES
VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
(SEQ ID NO: 112).

[000312] The invention further includes humanized antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:
EVQLVESGGGLVQPGGSLRLSCAVSGIDVTNYYMQWVRQAPGKGLEWVGVIGVN
GKRYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT
VSS (SEQ ID NO: 113).

[000313] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below:
EVQLVESGGGLVQPGGSLRLSCAVSGIDVTNYYMQWVRQAPGKGLEWVGVIGVN
GKRYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF

PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 114).

[000314] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 115; SEQ ID NO: 116; and SEQ ID NO: 117 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 111 or the light chain sequence of SEQ ID NO: 112, and/or one or more of the polypeptide sequences of SEQ ID NO: 118; SEQ ID NO: 119; and SEQ ID NO: 120 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 113 or the heavy chain sequence of SEQ ID NO: 114, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000315] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 111 or SEQ ID NO: 112. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 113 or SEQ ID NO: 114.

[000316] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID

NO: 115; SEQ ID NO: 116; and SEQ ID NO: 117 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 111 or the light chain sequence of SEQ ID NO: 112.

[000317] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 118; SEQ ID NO: 119; and SEQ ID NO: 120 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 113 or the heavy chain sequence of SEQ ID NO: 114.

[000318] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 111; the variable heavy chain region of SEQ ID NO: 113; the complementarity-determining regions (SEQ ID NO: 115; SEQ ID NO: 116; and SEQ ID NO: 117) of the variable light chain region of SEQ ID NO: 111; and the complementarity-determining regions (SEQ ID NO: 118; SEQ ID NO: 119; and SEQ ID NO: 120) of the variable heavy chain region of SEQ ID NO: 113.

[000319] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab12, comprising, or alternatively consisting of, SEQ ID NO: 112 and SEQ ID NO: 114, and having at least one of the biological activities set forth herein.

[000320] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab12, the Fab fragment for the treatment or prevention of CGRP-associated diarrhea includes the variable light chain sequence of

SEQ ID NO: 111 and the variable heavy chain sequence of SEQ ID NO: 113. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 111 and/or SEQ ID NO: 113 in said Fab while retaining binding specificity for CGRP.

[000321] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab12. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab12 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab13

[000322] In one embodiment, the invention includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: AIVMTQTPSSKSVPVGDTVTINCQASESLYNNNALAWFQQKPGQPPKRLIYDASKL ASGVPSRFSGGGSGTQFTLTISGVQCDDAATYYCGGYRSDSVDGVAFAGGTEVVV KR (SEQ ID NO: 121).

[000323] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below: AIVMTQTPSSKSVPVGDTVTINCQASESLYNNNALAWFQQKPGQPPKRLIYDASKL ASGVPSRFSGGGSGTQFTLTISGVQCDDAATYYCGGYRSDSVDGVAFAGGTEVVV KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 122).

[000324] The invention further includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and

possessing a variable heavy chain sequence comprising the sequence set forth below: QSVEESGGGLVQPEGSLTLTCTASGFDFSSNAMWWVRQAPGKGLEWIGIIYNGDG STYYASWVNGRFSISKTSSTTVTLQLNSLTVADTATYYCARDLDLWGPGTLVTVS S (SEQ ID NO: 123).

[000325] The invention also includes chimeric antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: QSVEESGGGLVQPEGSLTLTCTASGFDFSSNAMWWVRQAPGKGLEWIGCIYNGD GSTYYASWVNGRFSISKTSSTTVTLQLNSLTVADTATYYCARDLDLWGPGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 124).

[000326] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 125; SEQ ID NO: 126; and SEQ ID NO: 127 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 121 or the light chain sequence of SEQ ID NO: 122, and/or one or more of the polypeptide sequences of SEQ ID NO: 128; SEQ ID NO: 129; and SEQ ID NO: 130 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123 or the heavy chain sequence of SEQ ID NO: 124, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000327] The invention also contemplates fragments of the antibody for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 121 or SEQ ID NO: 122. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 123 or SEQ ID NO: 124.

[000328] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 125; SEQ ID NO: 126; and SEQ ID NO: 127 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 121 or the light chain sequence of SEQ ID NO: 122.

[000329] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 128; SEQ ID NO: 129; and SEQ ID NO: 130 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 123 or the heavy chain sequence of SEQ ID NO: 124.

[000330] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 121; the variable heavy chain region of SEQ ID NO: 123; the complementarity-determining regions (SEQ ID NO: 125; SEQ ID NO: 126; and SEQ ID NO: 127) of the variable light chain region of SEQ ID NO: 121; and the complementarity-determining regions (SEQ ID NO: 128; SEQ ID NO: 129; and SEQ ID NO: 130) of the variable heavy chain region of SEQ ID NO: 123.

[000331] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab13, comprising, or alternatively consisting of, SEQ ID NO: 122 and SEQ ID NO: 124, and having at least one of the biological activities set forth herein.

[000332] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab13, the Fab fragment for the treatment or prevention of CGRP-associated diarrhea includes the variable light chain sequence of SEQ ID NO: 121 and the variable heavy chain sequence of SEQ ID NO: 123. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 121 and/or SEQ ID NO: 123 in said Fab while retaining binding specificity for CGRP.

[000333] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab13. In another embodiment of the invention, anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea such as Ab13 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab14

[000334] In one embodiment, the invention includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSRGDCFVFGGGTKVEIK R (SEQ ID NO: 131).

[000335] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and

possessing a light chain sequence comprising the sequence set forth below: QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTL ASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCSRGDCFVFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 132).

[000336] The invention further includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSD GKTYYATWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCTRGDIWGQGTLVT VSS (SEQ ID NO: 133).

[000337] The invention also includes humanized antibodies for the treatment or prevention of CGRP-associated diarrhea having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below: EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSD GKTYYATWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCTRGDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 134).

[000338] The invention further contemplates antibodies for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the polypeptide sequences of SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 131 or the light chain sequence of SEQ ID NO: 132, and/or one or more of the polypeptide sequences of SEQ ID NO: 138; SEQ ID NO: 139;

and SEQ ID NO: 140 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 133 or the heavy chain sequence of SEQ ID NO: 134, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

[000339] The invention also contemplates fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea. In one embodiment of the invention, antibody fragments of the invention for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 131 or SEQ ID NO: 132. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 133 or SEQ ID NO: 134.

[000340] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 131 or the light chain sequence of SEQ ID NO: 132.

[000341] In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 138; SEQ ID NO: 139; and SEQ ID NO: 140 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 133 or the heavy chain sequence of SEQ ID NO: 134.

[000342] The invention also contemplates antibody fragments for the treatment or prevention of CGRP-associated diarrhea which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the

antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 131; the variable heavy chain region of SEQ ID NO: 133; the complementarity-determining regions (SEQ ID NO: 135; SEQ ID NO: 136; and SEQ ID NO: 137) of the variable light chain region of SEQ ID NO: 131; and the complementarity-determining regions (SEQ ID NO: 138; SEQ ID NO: 139; and SEQ ID NO: 140) of the variable heavy chain region of SEQ ID NO: 133.

[000343] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is Ab14, comprising, or alternatively consisting of, SEQ ID NO: 132 and SEQ ID NO: 134, and having at least one of the biological activities set forth herein.

[000344] In a further particularly preferred embodiment of the invention, antibody fragments for the treatment or prevention of CGRP-associated diarrhea comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab14, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 131 and the variable heavy chain sequence of SEQ ID NO: 133. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 131 and/or SEQ ID NO: 133 in said Fab while retaining binding specificity for CGRP.

[000345] In one embodiment of the invention described herein (infra), Fab fragments for the treatment or prevention of CGRP-associated diarrhea may be produced by enzymatic digestion (e.g., papain) of Ab14. In another embodiment of the invention, anti-CGRP antibodies such as Ab14 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[000346] In another embodiment, antibody fragments may be present in one or more of the following non-limiting forms: Fab, Fab', F(ab')2, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-CGRP antibodies described herein for the

treatment or prevention of CGRP-associated diarrhea further comprises the kappa constant light chain sequence comprising the sequence set forth below:

[000347] VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 283).

[000348] In another preferred embodiment, the anti-CGRP antibodies described herein for the treatment or prevention of CGRP-associated diarrhea further comprises the gamma-1 constant heavy chain polypeptide sequence comprising the sequence set forth below:

[000349] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK (SEQ ID NO: 284).

[000350] In another embodiment, the invention contemplates an isolated anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea comprising a VH polypeptide sequence selected from: SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, or 133, or a variant thereof; and further comprising a VL polypeptide sequence selected from: SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, or 131, or a variant thereof, wherein one or more of the framework residues (FR residues) in said VH or VL polypeptide has been substituted with another amino acid residue resulting in an anti-CGRP antibody that specifically binds CGRP. The invention contemplates humanized and chimeric forms of these antibodies for the treatment or prevention of CGRP-associated diarrhea. The chimeric antibodies may include an Fc derived from IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, IgG7, IgG8, IgG9, IgG10, IgG11, IgG12, IgG13, IgG14, IgG15, IgG16, IgG17, IgG18 or IgG19 constant regions.

[000351] In one embodiment of the invention, the antibodies or VH or VL polypeptides for the treatment or prevention of CGRP-associated diarrhea originate or are selected from

one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

[000352] In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof for the treatment or prevention of CGRP-associated diarrhea do not have binding specificity for CGRP-R. In a further embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association of CGRP with CGRP-R. In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof for the treatment or prevention of CGRP-associated diarrhea inhibit the association of CGRP with CGRP-R and/or additional proteins and/or multimers thereof, and/or antagonizes the biological effects thereof.

[000353] As stated in paragraph [0127] herein, antibodies and fragments thereof for the treatment or prevention of CGRP-associated diarrhea may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[000354] Antibodies or fragments thereof may also be chemically modified to provide additional advantages such as increased solubility, stability and circulating time (in vivo half-life) of the polypeptide, or decreased immunogenicity (See U.S. Pat. No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies and fragments thereof may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[000355] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired

therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., Appl. Biochem. Biotechnol. 56:59-72 (1996); Vorobjev et al., Nucleosides Nucleotides 18:2745-2750 (1999); and Caliceti et al., Bioconjug. Chem. 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[000356] There are a number of attachment methods available to those skilled in the art, See e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), See also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[000357] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to polypeptides via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid,

glutamic acid, or cysteine) or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof).

[000358] Alternatively, antibodies or fragments thereof for the treatment or prevention of CGRP-associated diarrhea may have increased in vivo half lives via fusion with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (See, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)) or other circulating blood proteins such as transferrin or ferritin. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[000359] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, beta-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. Further exemplary radioactive materials include, but are not limited to, Iodine 125 (125I), Carbon 14 (14C), Sulfur 35 (35S), Tritium (3H) and Phosphorus 32 (32P).

[000360] Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclothosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and

bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimytotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, pseudomonas exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[000361] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine and bleomycin. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and Pseudomonas toxin may be conjugated to the humanized or chimeric antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents (Youle, et al., Proc. Nat'l Acad. Sci. USA 77:5483 (1980); Gilliland, et al., Proc. Nat'l Acad. Sci. USA 77:4539 (1980); Krolick, et al., Proc. Nat'l Acad. Sci. USA 77:5419 (1980)).

[000362] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32 (32P), Scandium-47 (47Sc), Copper-67 (67Cu), Gallium-67 (67Ga), Yttrium-88 (88Y), Yttrium-90 (90Y), Iodine-125 (125I), Iodine-131 (131I), Samarium-153 (153Sm), Lutetium-177 (177Lu), Rhenium-186 (186Re) or Rhenium-188 (188Re), and alpha-emitters such as Astatine-211 (211At), Lead-212 (212Pb), Bismuth-212 (212Bi) or -213 (213Bi) or Actinium-225 (225Ac).

[000363] Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter et al, Nature 144:945 (1962); David et al, Biochemistry 13:1014 (1974); Pain et al,

J. Immunol. Meth. 40:219 (1981); and Nygren, J., Histochem. and Cytochem. 30:407 (1982).

[000364] Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camelbodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, e.g., conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, e.g., one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

[000365] In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

[000366] In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-CGRP activity. Non-limiting examples of anti-CGRP activity are set forth herein, for example, in paragraphs [0329]-[0350] infra.

[000367] In another embodiment, the invention further contemplates the generation and use of anti-idiotypic antibodies that bind any of the foregoing sequences. In an exemplary embodiment, such an anti-idiotypic antibody could be administered to a subject who has received an anti-CGRP antibody to modulate, reduce, or neutralize, the effect of the anti-CGRP antibody. Such anti-idiotypic antibodies could also be useful for treatment of an autoimmune disease characterized by the presence of anti-CGRP antibodies. A further

exemplary use of such anti-idiotypic antibodies is for detection of the anti-CGRP antibodies of the present invention, for example to monitor the levels of the anti-CGRP antibodies present in a subject's blood or other bodily fluids.

[000368] The present invention also contemplates anti-CGRP antibodies comprising any of the polypeptide or polynucleotide sequences described herein substituted for any of the other polynucleotide sequences described herein. For example, without limitation thereto, the present invention contemplates antibodies comprising the combination of any of the variable light chain and variable heavy chain sequences described herein, and further contemplates antibodies resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein.

Additional Exemplary Embodiments of the Invention

[000369] In another embodiment, the invention contemplates one or more anti-human CGRP antibodies or antibody fragments thereof for the treatment or prevention of CGRP-associated diarrhea which specifically bind to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human CGRP polypeptide or fragment thereof as an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14. In a preferred embodiment, the anti-human CGRP antibody or fragment thereof specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on an intact human CGRP polypeptide or a fragment thereof as Ab3, Ab6, Ab13, Ab12 or Ab14.

[000370] A preferred embodiment of the invention is directed to chimeric or humanized antibodies and fragments thereof (including Fab fragments) having binding specificity for CGRP and inhibiting biological activities mediated by the binding of CGRP to the CGRP receptor for the treatment or prevention of CGRP-associated diarrhea. In a particularly preferred embodiment of the invention, the chimeric or humanized anti-CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea are selected from Ab3, Ab6, Ab10, Ab13, or Ab14.

[000371] A preferred embodiment of the invention is directed to methods of screening antibodies and fragments thereof (including Fab fragments) having binding specificity to

human Calcitonin Gene Related Peptide (hereinafter "CGRP") in animal models to determine the in vivo effects thereof, especially their ability to antagonize the adverse side effects of CGRP including CGRP-associated diarrhea and to treat conditions involving excess CGRP.

[000372] Another more specific preferred embodiment of the invention involves a method of assessing the potential in vivo efficacy of a candidate anti-CGRP antibody or antibody fragment comprising determining whether the antibody inhibits CGRP associated diarrhea compared to a rodent administered CGRP in the absence of the candidate CGRP antibody or antibody fragment.

[000373] A more specific preferred embodiment of the invention involves a method of assessing the potential in vivo efficacy of a candidate anti-CGRP antibody or antibody fragment to treat a neurological condition characterized by increased CGRP levels.

[000374] Another more specific preferred embodiment of the invention involves a method of assessing the potential in vivo efficacy of a candidate anti-CGRP antibody or antibody fragment to treat a CGRP associated disorder associated with diarrhea such as migraine or chronic migraine, (with or without aura), weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, hemiplagic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysomal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (such as for example associated with sinusitis), allergy-induced headaches or migraines, pain, inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary or metastatic bone cancer pain, fracture pain, chronic pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, abdominal pain, pain associated with sickle cell crises, and other nociceptic pain, as well as hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptic pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, or pain or visceral pain associated with: gastro-esophageal

reflux, dyspepsia, irritable bowel syndrome, irritable colon, spastic colon, mucous colitis, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, pancreatitis, renal colic, dysmenorrhea, cystitis, including interstitial cystitis (IC), surgery associated with the ileus, diverticulitis, peritonitis, pericarditis, hepatitis, appendicitis, colitis, cholecystitis, endometriosis, chronic and/or acute pancreatitis, myocardial infarction, kidney pain, pleural pain, prostatitis, pelvic pain, trauma to an organ, chronic nociceptive pain, chronic neuropathic pain, chronic inflammatory pain, fibromyalgia, breakthrough pain and persistent pain.

[000375] Another more specific preferred embodiment of the invention involves a method of using an anti-CGRP antibody or antibody fragment to treat a CGRP associated disorder associated with diarrhea wherein the condition is cancer pain arising from malignancy or from cancer preferably selected from one or more of: adenocarcinoma in glandular tissue, blastoma in embryonic tissue of organs, carcinoma in epithelial tissue, leukemia in tissues that form blood cells, lymphoma in lymphatic tissue, myeloma in bone marrow, sarcoma in connective or supportive tissue, adrenal cancer, AIDS-related lymphoma, anemia, bladder cancer, bone cancer, brain cancer, breast cancer, carcinoid tumours, cervical cancer, chemotherapy, colon cancer, cytopenia, endometrial cancer, esophageal cancer, gastric cancer, head cancer, neck cancer, hepatobiliary cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, Hodgkin's disease, lymphoma, non- Hodgkin's, nervous system tumours, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, thyroid cancer, urethral cancer, bone cancer, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells, cancer of bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer, tumours that metastasize to the bone, tumours infiltrating the nerve and hollow viscus, tumours near neural structures. Further preferably the cancer pain comprises visceral pain, preferably visceral pain which arises from pancreatic cancer and/or metastases in the abdomen. Further preferably the cancer pain comprises somatic pain, preferably somatic pain due to one or more of bone cancer, metastasis in the bone, postsurgical pain, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of

blood-forming cells of the bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer.

[000376] A further another preferred embodiment of the invention relates to methods of inhibiting, preventing or treating diarrhea and/or maintaining electrolyte balance and fluid levels in the intestines of a subject having a condition associated with elevated CGRP levels that result in diarrhea and/or increased flux of electrolytes and fluids from the intestines comprising administering an effective amount of an anti-CGRP antibody or anti-CGRP antibody fragment.

[000377] Related thereto another preferred embodiment of the invention specifically relates to methods of treating or preventing diarrhea in individuals with functional bowel disorders or an inflammatory bowel diseases, bacterial or viral induced diarrhea, cancer associated with diarrhea, such as medullary thyroid carcinoma or a colorectal cancer, and more specifically functional bowel disorders or inflammatory bowel diseases, including by way of example gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, diverticulosis, and diverticulitis or inflammatory bowel disease is selected from the group consisting of Crohn's disease, ileitis, collagenous colitis, lymphocytic colitis, and ulcerative colitis wherein these therapies administer an effective amount of an anti-CGRP antibody or antibody fragment administered as a monotherapy or in combination with another active agent.

[000378] Other preferred embodiments the present invention are directed to screening assays and therapeutic usage of specific antibodies and fragments thereof having binding specificity for CGRP, in particular antibodies having desired epitopic specificity, high affinity or avidity and/or functional properties. In preferred embodiments this invention relates to assays and usage of the antibodies described herein, comprising the sequences of the VH, VL and CDR polypeptides described herein, and the polynucleotides encoding them. A preferred embodiment of the invention is directed to chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP and/or inhibiting the biological activities mediated by the binding of CGRP to the CGRP receptor ("CGRP-R").

[000379] In a further embodiment of the invention is contemplated a method of reducing, treating or preventing diseases or disorders associated with CGRP which may include diarrhea as an adverse side effect by affecting those biological activities mediated via CGRP, thereby avoiding the biological activities mediated via binding of CGRP to CGRP-R. A further non-limiting listing of diseases and disorders associated with CGRP is provided herein.

[000380] In another embodiment of the invention, the anti-human CGRP antibody for the treatment or prevention of CGRP-associated diarrhea is an antibody which specifically binds to the same linear or conformational epitopes on an intact CGRP polypeptide or fragment thereof that is (are) specifically bound by Ab3, Ab6, Ab13, or Ab14 as ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human CGRP polypeptide.

[000381] The invention is also directed to an anti-CGRP antibody for the treatment or prevention of CGRP-associated diarrhea that binds with the same CGRP epitope and/or competes with an anti-CGRP antibody for binding to CGRP as an antibody or antibody fragment disclosed herein, including but not limited to an anti-CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14.

[000382] In another embodiment, the invention is also directed to an isolated anti-CGRP antibody or antibody fragment for the treatment or prevention of CGRP-associated diarrhea comprising one or more of the CDRs contained in the VH polypeptide sequences selected from: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, or 133, or a variant thereof, and/or one or more of the CDRs contained in the VL polypeptide sequences selected from: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, or 131, or a variant thereof.

[000383] In one embodiment of the invention, the anti-human CGRP antibody discussed in the two prior paragraphs comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14.

[000384] In a preferred embodiment, the anti-human CGRP antibody discussed above comprises at least 2 complementarity determining regions (CDRs) in each the variable light

and the variable heavy regions which are identical to those contained in Ab3 or Ab6. In another embodiment, all of the CDRs of the anti-human CGRP antibody discussed above are identical to the CDRs contained in an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14. In a preferred embodiment of the invention, all of the CDRs of the anti-human CGRP antibody discussed above are identical to the CDRs contained in an anti-human CGRP antibody selected from Ab3 or Ab6.

[000385] The invention further contemplates that the one or more anti-human CGRP antibodies discussed above for the treatment or prevention of CGRP-associated diarrhea which are aglycosylated; or minimally glycosylated, e.g., which lack N-glycosylation but may comprise some O-glycosylation, such as mannose residues, and/or that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-human CGRP antibody.

[000386] The invention further contemplates one or more anti-human CGRP antibodies for the treatment or prevention of CGRP-associated diarrhea wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of one or more human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library.

[000387] In one embodiment of the invention, the anti-human CGRP antibody or fragment for the treatment or prevention of CGRP-associated diarrhea specifically binds to CGRP expressing human cells and/or to circulating soluble CGRP molecules in vivo, including CGRP expressed on or by human cells in a patient with a disease associated with cells that express CGRP.

[000388] In another embodiment, the CGRP related disease that may be associated with diarrhea is selected from migraines (with or without aura), weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, hemiplagic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysomal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (such as for example associated with sinusitis), allergy-induced headaches or migraines, pain, inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary or metastatic bone cancer pain, fracture pain, chronic pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, abdominal pain, pain associated with sickle cell crises, and other nociceptic pain, as well as hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptic pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, or pain or visceral pain associated with: gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, irritable colon, spastic colon, mucous colitis, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, pancreatitis, renal colic, dysmenorrhea, cystitis, including interstitial cystitis (IC), surgery associated with the ileus, diverticulitis, peritonitis, pericarditis, hepatitis, appendicitis, colitis, cholecystitis, endometriosis, chronic and/or acute pancreatitis, myocardial infarction, kidney pain, pleural pain, prostatitis, pelvic pain, trauma to an organ, chronic nociceptive pain, chronic neuropathic pain, chronic inflammatory pain, fibromyalgia, breakthrough pain and persistent pain.

[000389] In another embodiment of the invention, the disease treated that may be associated with diarrhea is cancer pain arising from malignancy or from cancer preferably selected from one or more of: adenocarcinoma in glandular tissue, blastoma in embryonic tissue of organs, carcinoma in epithelial tissue, leukemia in tissues that form blood cells, lymphoma in lymphatic tissue, myeloma in bone marrow, sarcoma in connective or

supportive tissue, adrenal cancer, AIDS-related lymphoma, anemia, bladder cancer, bone cancer, brain cancer, breast cancer, carcinoid tumours, cervical cancer, chemotherapy, colon cancer, cytopenia, , endometrial cancer, esophageal cancer, gastric cancer, head cancer, neck cancer, hepatobiliary cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, Hodgkin's disease, lymphoma, non- Hodgkin's, nervous system tumours, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, thyroid cancer, urethral cancer, bone cancer, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells, cancer of bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer, tumours that metastasize to the bone, tumours infiltrating the nerve and hollow viscus, tumours near neural structures. Further preferably the cancer pain comprises visceral pain, preferably visceral pain which arises from pancreatic cancer and/or metastases in the abdomen. Further preferably the cancer pain comprises somatic pain, preferably somatic pain due to one or more of bone cancer, metastasis in the bone, postsurgical pain, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells of the bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer.

[000390] The invention further contemplates anti-human CGRPantibodies or fragments diarrhea directly or indirectly attached to a detectable label or therapeutic agent.

[000391] The invention also contemplates one or more nucleic acid sequences which result in the expression of an anti-human CGRP antibody or antibody fragment as set forth above, including those comprising, or alternatively consisting of, yeast or human preferred codons. The invention also contemplates vectors (including plasmids or recombinant viral vectors) comprising said nucleic acid sequence(s). The invention also contemplates host cells or recombinant host cells expressing at least one of the antibodies set forth above, including a mammalian, yeast, bacterial, and insect cells. In a preferred embodiment, the host cell is a yeast cell. In a further preferred embodiment, the yeast cell is a diploidal yeast cell. In a more preferred embodiment, the yeast cell is a Pichia yeast.

[000392] The invention also contemplates a method of treatment comprising administering to a patient with a disease or condition associated with CGRP expressing cells that results

in diarrhea a therapeutically effective amount of at least one anti-human CGRP antibody or fragment described herein. The invention also contemplates that the treatment method may involve the administration of two or more anti-CGRP antibodies or fragments thereof and disclosed herein. If more than one antibody is administered to the patient, the multiple antibodies may be administered simultaneously or concurrently, or may be staggered in their administration. The diseases that may be treated are presented in the non-limiting list set forth above and elsewhere herein. In a preferred embodiment, the disease is selected from migraine, headache, weight loss, pain, cancer pain or neuropathic pain. In another embodiment the treatment further includes the administration of another therapeutic agent or regimen selected from chemotherapy, radiotherapy, cytokine administration or gene therapy.

[000393] In a non-limiting embodiment of the invention, another therapeutic agent or regimen includes opioids, analgesics such as NSAIDs, Taxol (paclitaxel) or its derivatives, platinum compounds such as carboplatin or cisplatin, anthrocyclines such as doxorubicin, alkylating agents such as cyclophosphamide, anti-metabolites such as 5-fluorouracil, or etoposide.

[000394] The invention further contemplates a method of in vivo imaging which detects the presence of cells which express CGRP comprising administering a diagnostically effective amount of at least one anti-human CGRP antibody. In one embodiment, said administration further includes the administration of a radionuclide or fluorophore that facilitates detection of the antibody at CGRP expressing disease sites. In a further embodiment, the results of said in vivo imaging method are used to facilitate the design of an appropriate therapeutic regimen, including therapeutic regimens including radiotherapy, chemotherapy or a combination thereof.

[000395] The anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP diarrhea, may also be described by their strength of binding or their affinity for CGRP. In one embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with a dissociation constant (KD) of less than or equal to 5x10-7 M, 10-7 M, 5x10-8 M, 10-8 M, 5x10-9 M, 10-9 M, 5x10-10 M, 10-10

M, 5x10-11 M, 10-11 M, 5x10-12 M, 10-12 M, 5x10-13 M, or 10-13 M. Preferably, the anti-CGRP antibodies and fragments thereof bind CGRP with a dissociation constant of less than or equal to 10-11 M, 5x10-12 M, or 10-12 M. In another embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to a linear or conformational CGRP epitope.

[000396] In another embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with an off-rate of less than or equal to 10-4 S-1, 5x10-5 S-1, 10-5 S-1, 5x10-6 S-1, 10-6 S-1, 5x10-7 S-1, or 10-7 S-1.

[000397] In a further embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, exhibit anti-CGRP activity by preventing, ameliorating or reducing the symptoms of, or alternatively treating, diseases and disorders associated with CGRP especially diarrhea. Non-limiting examples of diseases and disorders associated with CGRP are set forth herein.

Polynucleotides Encoding Anti-CGRP Antibody Polypeptides

Antibody Ab1

[000398] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 1:

[000399] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG
CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACC
TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT
ACATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGG
GACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTA

CTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGG AGGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 141).

[000400] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 2:

[000401] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACC TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT ACATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGG GACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTA CTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGG AGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCT TCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGC TGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACA GCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAA ACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 142).

[000402] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 3:

[000403] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC CCTGACACTCACCTGCACAGTCTCTGGACTCGACCTCAGTAGCTACTACATGCA ATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTA TTAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC AGAGCCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA CACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACCCTCG TCACCGTCTCGAGC (SEQ ID NO: 143).

[000404] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 4:

[000405] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC
CCTGACACTCACCTGCACAGTCTCTGGACTCGACCTCAGTAGCTACTACATGCA
ATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTA
TTAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC
AGAGCCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 144).

[000406] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 145; SEQ ID NO: 146; and SEQ ID NO: 147 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 1 or the light chain sequence of SEQ ID NO: 2.

[000407] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 3 or the heavy chain sequence of SEQ ID NO: 4.

[000408] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 141 encoding the light chain variable sequence of SEQ ID NO: 1; the polynucleotide SEQ ID NO: 142 encoding the light chain sequence of SEQ ID NO: 2; the polynucleotide SEQ ID NO: 143 encoding the heavy chain variable sequence of SEQ ID NO: 3; the polynucleotide SEQ ID NO: 144 encoding the heavy chain sequence of SEQ ID NO: 4; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 145; SEQ ID NO: 146; and SEQ ID NO: 147) of the light chain variable sequence of SEQ ID NO: 1 or the light chain sequence of SEQ ID NO: 2; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 148; SEQ ID NO: 149; and SEQ ID NO: 150) of the heavy chain variable sequence of SEQ ID NO: 3 or the heavy chain sequence of SEQ ID NO: 4.

[000409] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab1,

the polynucleotides encoding the full length Ab1 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 142 encoding the light chain sequence of SEQ ID NO: 2 and the polynucleotide SEQ ID NO: 144 encoding the heavy chain sequence of SEQ ID NO: 4.

[000410] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab1 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab1 or Fab fragments thereof may be produced via expression of Ab1 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab2

[000411] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 11:

[000412] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATGATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagt tcctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTAGGCAGTTATGATT GTAGTAGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 151).

[000413] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 12:

[000414] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATGATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagt tcctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTAGGCAGTTATGATT GTAGTAGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTG CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTG CCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGT GGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCA AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 152).

[000415] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 13:

[000416] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaCTCGACCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCcg attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 153).

[000417] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 14:

[000418] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaCTCGACCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCcg

attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat
TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACCA
AGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCA
CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA
GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC
AAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC
ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAG
CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG
GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG
AGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 154).

[000419] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 155; SEQ ID NO: 156; and SEQ ID NO: 157 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 11 or the light chain sequence of SEQ ID NO: 12.

[000420] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 158; SEQ ID NO: 159; and SEQ ID

NO: 160 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 13 or the heavy chain sequence of SEQ ID NO: 14.

[000421] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 151 encoding the light chain variable sequence of SEQ ID NO: 11; the polynucleotide SEQ ID NO: 152 encoding the light chain sequence of SEQ ID NO: 12; the polynucleotide SEQ ID NO: 153 encoding the heavy chain variable sequence of SEQ ID NO: 13; the polynucleotide SEQ ID NO: 154 encoding the heavy chain sequence of SEQ ID NO: 14; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 155; SEQ ID NO: 156; and SEQ ID NO: 157) of the light chain variable sequence of SEQ ID NO: 11 or the light chain sequence of SEQ ID NO: 12; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 158; SEQ ID NO: 159; and SEQ ID NO: 160) of the heavy chain variable sequence of SEQ ID NO: 13 or the heavy chain sequence of SEQ ID NO: 14.

[000422] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab2, the polynucleotides encoding the full length Ab2 antibody comprise, or alternatively consist of,the polynucleotide SEQ ID NO: 152 encoding the light chain sequence of SEQ ID NO: 12 and the polynucleotide SEQ ID NO: 154 encoding the heavy chain sequence of SEQ ID NO: 14.

[000423] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by

enzymatic digestion (e.g., papain) of Ab2 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab2 or Fab fragments thereof may be produced via expression of Ab2 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab3

[000424] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 21:

[000425] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATGATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagt tcctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTAGGCAGTTATGATT GTAGTAGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 161).

[000426] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 22:

[000427] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATGATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagt tcctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTAGGCAGTTATGATT GTAGTAGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTG CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTG CCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGT

GGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 162).

[000428] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 23:

[000429] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt
ctggaCTCGACCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt
cGGAGTCATTGGTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCcg
attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat
TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 163).

[000430] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 24:

[000431] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt
ctggaCTCGACCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt
cGGAGTCATTGGTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCcg
attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat
TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACCA
AGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCA
CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA
GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC
AAGGTGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC
ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGT

GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAG
CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG
GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG
AGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 164).

[000432] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 165; SEQ ID NO: 166; and SEQ ID NO: 167 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 21 or the light chain sequence of SEQ ID NO: 22.

[000433] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 168; SEQ ID NO: 169; and SEQ ID NO: 170 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 23 or the heavy chain sequence of SEQ ID NO: 24.

[000434] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 161 encoding the light chain variable sequence of SEQ ID NO: 21; the polynucleotide SEQ ID NO: 162 encoding the light chain sequence of SEQ ID

NO: 22; the polynucleotide SEQ ID NO: 163 encoding the heavy chain variable sequence of SEQ ID NO: 23; the polynucleotide SEQ ID NO: 164 encoding the heavy chain sequence of SEQ ID NO: 24; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 165; SEQ ID NO: 166; and SEQ ID NO: 167) of the light chain variable sequence of SEQ ID NO: 21 or the light chain sequence of SEQ ID NO: 22; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 168; SEQ ID NO: 169; and SEQ ID NO: 170) of the heavy chain variable sequence of SEQ ID NO: 23 or the heavy chain sequence of SEQ ID NO: 24.

[000435] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab3, the polynucleotides encoding the full length Ab3 antibody comprise, or alternatively consist of,the polynucleotide SEQ ID NO: 162 encoding the light chain sequence of SEQ ID NO: 22 and the polynucleotide SEQ ID NO: 164 encoding the heavy chain sequence of SEQ ID NO: 24.

[000436] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab3 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab3 or Fab fragments thereof may be produced via expression of Ab3 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab4

[000437] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 31:

[000438] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAACAACTGATCTATGATG CATCCACTCTGGCGTCTGGGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGGCGTGCAGTGTAACGATGCTGCCGCTTAC TACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 171).

[000439] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 32:

[000440] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAACAACTGATCTATGATG CATCCACTCTGGCGTCTGGGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGGCGTGCAGTGTAACGATGCTGCCGCTTAC TACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 172).

[000441] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 33:

[000442] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC
CCTGACACTCACCTGTTCCGTCTCTGGCATCGACCTCAGTGGCTACTACATGAA
CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTA
TTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC
AAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCGGGCACCCTCG
TCACCGTCTCGAGC (SEQ ID NO: 173).

[000443] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 34:

[000444] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC
CCTGACACTCACCTGTTCCGTCTCTGGCATCGACCTCAGTGGCTACTACATGAA
CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTA
TTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC
AAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCGGGCACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG

TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 174).

[000445] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 31 or the light chain sequence of SEQ ID NO: 32.

[000446] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 178; SEQ ID NO: 179; and SEQ ID NO: 180 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 33 or the heavy chain sequence of SEQ ID NO: 34.

[000447] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 171 encoding the light chain variable sequence of SEQ ID NO: 31; the polynucleotide SEQ ID NO: 172 encoding the light chain sequence of SEQ ID NO: 32; the polynucleotide SEQ ID NO: 173 encoding the heavy chain variable sequence of SEQ ID NO: 33; the polynucleotide SEQ ID NO: 174 encoding the heavy chain

sequence of SEQ ID NO: 34; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 175; SEQ ID NO: 176; and SEQ ID NO: 177) of the light chain variable sequence of SEQ ID NO: 31 or the light chain sequence of SEQ ID NO: 32; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 178; SEQ ID NO: 179; and SEQ ID NO: 180) of the heavy chain variable sequence of SEQ ID NO: 33 or the heavy chain sequence of SEQ ID NO: 34.

[000448] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab4, the polynucleotides encoding the full length Ab4 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 172 encoding the light chain sequence of SEQ ID NO: 32 and the polynucleotide SEQ ID NO: 174 encoding the heavy chain sequence of SEQ ID NO: 34.

[000449] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab4 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab4 or Fab fragments thereof may be produced via expression of Ab4 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab5

[000450] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following

polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 41:

[000451] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatGATGCATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATT GTACTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 181).

[000452] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 42:

[000453] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatGATGCATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATT GTACTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTG CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTG CCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGT GGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCA AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 182).

[000454] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 43:

[000455] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACCTCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCcg attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat

TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 183).

[000456] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 44:

[000457] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACCTCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCcg attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACCA AGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC AAAACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGT GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAG CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 184).

[000458] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 185; SEQ ID NO: 186; and SEQ ID NO: 187 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 41 or the light chain sequence of SEQ ID NO: 42.

[000459] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 43 or the heavy chain sequence of SEQ ID NO: 44.

[000460] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 181 encoding the light chain variable sequence of SEQ ID NO: 41; the polynucleotide SEQ ID NO: 182 encoding the light chain sequence of SEQ ID NO: 42; the polynucleotide SEQ ID NO: 183 encoding the heavy chain variable sequence of SEQ ID NO: 43; the polynucleotide SEQ ID NO: 184 encoding the heavy chain sequence of SEQ ID NO: 44; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 185; SEQ ID NO: 186; and SEQ ID NO: 187) of the light chain variable sequence of SEQ ID NO: 41 or the light chain sequence of SEQ ID NO: 42; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 188; SEQ ID NO: 189; and SEQ ID NO: 190) of the heavy chain variable sequence of SEQ ID NO: 43 or the heavy chain sequence of SEQ ID NO: 44.

[000461] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab5,

the polynucleotides encoding the full length Ab5 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 182 encoding the light chain sequence of SEQ ID NO: 42 and the polynucleotide SEQ ID NO: 184 encoding the heavy chain sequence of SEQ ID NO: 44.

[000462] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab5 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab5 or Fab fragments thereof may be produced via expression of Ab5 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[000463] Antibody Ab6

[000464] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 51:

[000465] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatGATGCATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATT GTACTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 191).

[000466] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 52:

[000467] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTATCATAACACCTACCTGGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatGATGCATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctg ggacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATT GTACTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTG CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTG CCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGT GGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCA AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 192).

[000468] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 53:

[000469] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACCTCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCcg attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 193).

[000470] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 54:

[000471] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACCTCagtGGCTACTACATGAACtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCcg

attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat
TTCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACCA
AGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCA
CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA
GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC
AAGGTGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC
ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAG
CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG
GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG
AGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 194).

[000472] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 195; SEQ ID NO: 196; and SEQ ID NO: 197 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 51 or the light chain sequence of SEQ ID NO: 52.

[000473] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 198; SEQ ID NO: 199; and SEQ ID

NO: 200 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 53 or the heavy chain sequence of SEQ ID NO: 54.

[000474] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 191 encoding the light chain variable sequence of SEQ ID NO: 51; the polynucleotide SEQ ID NO: 192 encoding the light chain sequence of SEQ ID NO: 52; the polynucleotide SEQ ID NO: 193 encoding the heavy chain variable sequence of SEQ ID NO: 53; the polynucleotide SEQ ID NO: 194 encoding the heavy chain sequence of SEQ ID NO: 54; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 195; SEQ ID NO: 196; and SEQ ID NO: 197) of the light chain variable sequence of SEQ ID NO: 51 or the light chain sequence of SEQ ID NO: 52; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 198; SEQ ID NO: 199; and SEQ ID NO: 200) of the heavy chain variable sequence of SEQ ID NO: 53 or the heavy chain sequence of SEQ ID NO: 54.

[000475] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the polynucleotides encoding the full length Ab6 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 192 encoding the light chain sequence of SEQ ID NO: 52 and the polynucleotide SEQ ID NO: 194 encoding the heavy chain sequence of SEQ ID NO: 54.

[000476] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by

enzymatic digestion (e.g., papain) of Ab6 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab fragments thereof may be produced via expression of Ab6 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab7

[000477] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 61:

[000478] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATAATTACAACTACCT TGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC TACTGTCTAGGCAGTTATGACTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 201).

[000479] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 62:

[000480] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATAATTACAACTACCT TGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC TACTGTCTAGGCAGTTATGACTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGA

GGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 202).

[000481] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 63:

[000482] CAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CATCCCTGACACTCACCTGCACCGTCTCTGGAATCGACCTCAGTAACCACTACA
TGCAATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCGTT
GGTATTAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCAT
CTCCAGAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGGCTGACAACCG
AGGACACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACC
CTGGTCACCGTCTCGAGC (SEQ ID NO: 203).

[000483] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 64:

[000484] CAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CATCCCTGACACTCACCTGCACCGTCTCTGGAATCGACCTCAGTAACCACTACA
TGCAATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCGTT
GGTATTAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCAT
CTCCAGAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGGCTGACAACCG
AGGACACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACC
CTGGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCA
cCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAA
GGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCA
GCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCA

GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGC
AACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCA
AATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTG
GGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATC
TCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCC
TGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA
CAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTC
ACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTC
CAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGC
AGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACC
AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACG
CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA
GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GA (SEQ ID NO: 204).

[000485] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 205; SEQ ID NO: 206; and SEQ ID NO: 207 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 61 or the light chain sequence of SEQ ID NO: 62.

[000486] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 208; SEQ ID NO: 209; and SEQ ID NO: 210 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 63 or the heavy chain sequence of SEQ ID NO: 64.

[000487] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In

one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 201 encoding the light chain variable sequence of SEQ ID NO: 61; the polynucleotide SEQ ID NO: 202 encoding the light chain sequence of SEQ ID NO: 62; the polynucleotide SEQ ID NO: 203 encoding the heavy chain variable sequence of SEQ ID NO: 63; the polynucleotide SEQ ID NO: 204 encoding the heavy chain sequence of SEQ ID NO: 64; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 205; SEQ ID NO: 206; and SEQ ID NO: 207) of the light chain variable sequence of SEQ ID NO: 61 or the light chain sequence of SEQ ID NO: 62; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 208; SEQ ID NO: 209; and SEQ ID NO: 210) of the heavy chain variable sequence of SEQ ID NO: 63 or the heavy chain sequence of SEQ ID NO: 64.

[000488] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab7, the polynucleotides encoding the full length Ab7 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 202 encoding the light chain sequence of SEQ ID NO: 62 and the polynucleotide SEQ ID NO: 204 encoding the heavy chain sequence of SEQ ID NO: 64.

[000489] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab7 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab7 or Fab fragments thereof may be produced via expression of Ab7 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia)

and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab8

[000490] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 71:

[000491] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTAcAATTACAACTACCTTGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG TAGTACTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 211).

[000492] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 72:

[000493] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAGTGTTTAcAATTACAACTACCTTGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG TAGTACTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGC CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGC AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAA AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 212).

[000494] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 73:

[000495] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACCTCagtAACCACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCGTTGGTATcAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCcga ttcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtatT TCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 213).

[000496] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 74:

[000497] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACCTCagtAACCACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCGTTGGTATcAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCcga ttcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtatT TCtgtGCTAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACCAA GGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCAC AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGT CGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAA GGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCAC CGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAA AACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGTGG TGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCA CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGC AAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAA AACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGC

CCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC
AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC
GGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT
TCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC
TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAG
CCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 214).

[000498] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 71 or the light chain sequence of SEQ ID NO: 72.

[000499] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 218; SEQ ID NO: 219; and SEQ ID NO: 220 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 73 or the heavy chain sequence of SEQ ID NO: 74.

[000500] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 211 encoding the light chain variable sequence of SEQ ID NO: 71; the polynucleotide SEQ ID NO: 212 encoding the light chain sequence of SEQ ID NO: 72; the polynucleotide SEQ ID NO: 213 encoding the heavy chain variable sequence of SEQ ID NO: 73; the polynucleotide SEQ ID NO: 214 encoding the heavy chain sequence of SEQ ID NO: 74; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 215; SEQ ID NO: 216; and SEQ ID NO: 217) of the light chain variable sequence of SEQ ID NO: 71 or the light chain sequence of SEQ ID NO: 72; and

polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 218; SEQ ID NO: 219; and SEQ ID NO: 220) of the heavy chain variable sequence of SEQ ID NO: 73 or the heavy chain sequence of SEQ ID NO: 74.

[000501] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab8, the polynucleotides encoding the full length Ab8 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 212 encoding the light chain sequence of SEQ ID NO: 72 and the polynucleotide SEQ ID NO: 214 encoding the heavy chain sequence of SEQ ID NO: 74.

[000502] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab8 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab8 or Fab fragments thereof may be produced via expression of Ab8 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab9

[000503] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 81:

[000504] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTATAATAACAACTACC TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT ACGTCCACTCTGGCATCTGGGGTCTCATCGCGATTCAGAGGCAGTGGATCTGG GACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTT ACTACTGTCTAGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCG GAGGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 221).

[000505] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 82:

[000506] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTATAATAACAACTACC TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT ACGTCCACTCTGGCATCTGGGGTCTCATCGCGATTCAGAGGCAGTGGATCTGG GACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTT ACTACTGTCTAGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCG GAGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATC TTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTG CTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGC CCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGAC AGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGA AACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC ACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 222).

[000507] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 83:

[000508] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC CCTGACACTCACCTGCACAGTCTCTGGAATCGGCCTCAGTAGCTACTACATGCA GTGGGTCCGCCAGTCTCCAGGGAGGGGGCTGGAATGGATCGGAGTCATTGGTA GTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCC

AAGACCTCGTCGACCACGGTGGATCTGAGAATGGCCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTACCAGAGGGGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGC (SEQ ID NO: 223).

[000509] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 84:

[000510] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC
CCTGACACTCACCTGCACAGTCTCTGGAATCGGCCTCAGTAGCTACTACATGCA
GTGGGTCCGCCAGTCTCCAGGGAGGGGGCTGGAATGGATCGGAGTCATTGGTA
GTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCC
AAGACCTCGTCGACCACGGTGGATCTGAGAATGGCCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTACCAGAGGGGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT

CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 224).

[000511] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 225; SEQ ID NO: 226; and SEQ ID NO: 227 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 81 or the light chain sequence of SEQ ID NO: 82.

[000512] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 83 or the heavy chain sequence of SEQ ID NO: 84.

[000513] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 221 encoding the light chain variable sequence of SEQ ID NO: 81; the polynucleotide SEQ ID NO: 222 encoding the light chain sequence of SEQ ID NO: 82; the polynucleotide SEQ ID NO: 223 encoding the heavy chain variable sequence of SEQ ID NO: 83; the polynucleotide SEQ ID NO: 224 encoding the heavy chain sequence of SEQ ID NO: 84; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 225; SEQ ID NO: 226; and SEQ ID NO: 227) of the light chain variable sequence of SEQ ID NO: 81 or the light chain sequence of SEQ ID NO: 82; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 228; SEQ ID NO: 229; and SEQ ID NO: 230) of the heavy chain variable sequence of SEQ ID NO: 83 or the heavy chain sequence of SEQ ID NO: 84.

[000514] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab9, the polynucleotides encoding the full length Ab9 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 222 encoding the light chain sequence of SEQ ID NO: 82 and the polynucleotide SEQ ID NO: 224 encoding the heavy chain sequence of SEQ ID NO: 84.

[000515] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab9 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab9 or Fab fragments thereof may be produced via expression of Ab9 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab10

[000516] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 91:

[000517] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA
GGCCAGTCAGAATGTTTAcAATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagtt
cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg
gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG

TAGTCGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 231).

[000518] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 92:

[000519] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAATGTTTAcAATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG TAGTCGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGC CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGC AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAA AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 232).

[000520] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 93:

[000521] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGGCCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCcg attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat TTCtgtACCAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 233).

[000522] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 94:

[000523] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGGCCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCcg attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat TTCtgtACCAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACCA AGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCA CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC AAAACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGT GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAG CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 234).

[000524] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 235; SEQ ID NO: 236; and SEQ ID NO: 237 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 91 or the light chain sequence of SEQ ID NO: 92.

[000525] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 238; SEQ ID NO: 239; and SEQ ID NO:240 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 93 or the heavy chain sequence of SEQ ID NO: 94.

[000526] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 231 encoding the light chain variable sequence of SEQ ID NO: 91; the polynucleotide SEQ ID NO: 232 encoding the light chain sequence of SEQ ID NO: 92; the polynucleotide SEQ ID NO: 233 encoding the heavy chain variable sequence of SEQ ID NO: 93; the polynucleotide SEQ ID NO: 234 encoding the heavy chain sequence of SEQ ID NO: 94; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 235; SEQ ID NO: 236; and SEQ ID NO: 237) of the light chain variable sequence of SEQ ID NO: 91 or the light chain sequence of SEQ ID NO: 92; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 238; SEQ ID NO: 239; and SEQ ID NO: 240) of the heavy chain variable sequence of SEQ ID NO: 93 or the heavy chain sequence of SEQ ID NO: 94.

[000527] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab10, the polynucleotides encoding the full length Ab10 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 232 encoding the light chain sequence of SEQ ID NO: 92 and the polynucleotide SEQ ID NO: 234 encoding the heavy chain sequence of SEQ ID NO: 94.

[000528] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO,

NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab10 or Fab fragments thereof may be produced via expression of Ab10 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab11

[000529] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 101:

[000530] CAGGTGCTGACCCAGACTGCATCCCCCGTGTCTCCAGCTGTGGGAAG CACAGTCACCATCAATTGCCGGGCCAGTCAGAGTGTTTATTATAACAACTACCT AGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC TACTGTCTAGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 241).

[000531] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 102:

[000532] CAGGTGCTGACCCAGACTGCATCCCCCGTGTCTCCAGCTGTGGGAAG CACAGTCACCATCAATTGCCGGGCCAGTCAGAGTGTTTATTATAACAACTACCT AGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA

CATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGG
ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC
TACTGTCTAGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGA
GGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 242).

[000533] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 103:

[000534] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGAGGATC
CCTGACACTCACCTGCACAGTCTCTGGAATCGACGTCACTAACTACTATATGCA
ATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTG
TGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC
AAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTGCCAGAGGCGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGC (SEQ ID NO: 243).

[000535] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 104:

[000536] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGAGGATC
CCTGACACTCACCTGCACAGTCTCTGGAATCGACGTCACTAACTACTATATGCA
ATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTG
TGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC
AAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTGCCAGAGGCGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAcCCT

CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 244).

[000537] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 245; SEQ ID NO: 246; and SEQ ID NO: 247 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 101 or the light chain sequence of SEQ ID NO: 102.

[000538] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 248; SEQ ID NO: 249; and SEQ ID NO: 250 which correspond to polynucleotides encoding the complementarity-determining

regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 103 or the heavy chain sequence of SEQ ID NO: 104.

[000539] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 241 encoding the light chain variable sequence of SEQ ID NO: 101; the polynucleotide SEQ ID NO: 242 encoding the light chain sequence of SEQ ID NO: 102; the polynucleotide SEQ ID NO: 243 encoding the heavy chain variable sequence of SEQ ID NO: 103; the polynucleotide SEQ ID NO: 244 encoding the heavy chain sequence of SEQ ID NO: 104; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 245; SEQ ID NO: 246; and SEQ ID NO: 247) of the light chain variable sequence of SEQ ID NO: 101 or the light chain sequence of SEQ ID NO: 102; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 248; SEQ ID NO: 249; and SEQ ID NO: 250) of the heavy chain variable sequence of SEQ ID NO: 103 or the heavy chain sequence of SEQ ID NO: 104.

[000540] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab11, the polynucleotides encoding the full length Ab11 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 242 encoding the light chain sequence of SEQ ID NO: 102 and the polynucleotide SEQ ID NO: 244 encoding the heavy chain sequence of SEQ ID NO: 104.

[000541] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab11 following expression of the full-length

polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab11 or Fab fragments thereof may be produced via expression of Ab11 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab12

[000542] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 111:

[000543] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCG GGCCAGTCAGAGTGTTTAcTATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG TAGTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 251).

[000544] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 112:

[000545] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCG GGCCAGTCAGAGTGTTTAcTATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG TAGTAATGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGC CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGC

AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAA AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 252).

[000546] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 113:

[000547] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACGTCACTAACTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgg gtcGGAGTCATTGGTGTGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGC cgattcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgt atTTCtgtGCCAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 253).

[000548] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 114:

[000549] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGACGTCACTAACTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgg gtcGGAGTCATTGGTGTGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGC cgattcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgt atTTCtgtGCCAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACC AAGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGC ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGT GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC AAAACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGT GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG

GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAG
CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG
GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG
AGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 254).

[000550] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 111 or the light chain sequence of SEQ ID NO: 112.

[000551] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 258; SEQ ID NO: 259; and SEQ ID NO: 260 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 113 or the heavy chain sequence of SEQ ID NO: 114.

[000552] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 251 encoding the light chain variable sequence of SEQ ID NO: 111; the polynucleotide SEQ ID NO: 252 encoding the light chain sequence of SEQ ID NO: 112; the polynucleotide SEQ ID NO: 253 encoding the heavy chain variable

sequence of SEQ ID NO: 113; the polynucleotide SEQ ID NO: 254 encoding the heavy chain sequence of SEQ ID NO: 114; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 255; SEQ ID NO: 256; and SEQ ID NO: 257) of the light chain variable sequence of SEQ ID NO: 111 or the light chain sequence of SEQ ID NO: 112; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 258; SEQ ID NO: 259; and SEQ ID NO: 260) of the heavy chain variable sequence of SEQ ID NO: 113 or the heavy chain sequence of SEQ ID NO: 114.

[000553] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab12, the polynucleotides encoding the full length Ab12 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 252 encoding the light chain sequence of SEQ ID NO: 112 and the polynucleotide SEQ ID NO: 254 encoding the heavy chain sequence of SEQ ID NO: 114.

[000554] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab12 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab12 or Fab fragments thereof may be produced via expression of Ab12 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab13

[000555] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention,

polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 121:

[000556] GCCATCGTGATGACCCAGACTCCATCTTCCAAGTCTGTCCCTGTGGGA GACACAGTCACCATCAATTGCCAGGCCAGTGAGAGTCTTTATAATAACAACGC CTTGGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATG ATGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAGTGGCGGTGGGTCT GGGACACAGTTCACTCTCACCATCAGTGGCGTGCAGTGTGACGATGCTGCCAC TTACTACTGTGGAGGCTACAGAAGTGATAGTGTTGATGGTGTTGCTTTCGCCGG AGGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 261).

[000557] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 122:

[000558] GCCATCGTGATGACCCAGACTCCATCTTCCAAGTCTGTCCCTGTGGGA GACACAGTCACCATCAATTGCCAGGCCAGTGAGAGTCTTTATAATAACAACGC CTTGGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATG ATGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAGTGGCGGTGGGTCT GGGACACAGTTCACTCTCACCATCAGTGGCGTGCAGTGTGACGATGCTGCCAC TTACTACTGTGGAGGCTACAGAAGTGATAGTGTTGATGGTGTTGCTTTCGCCGG AGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCT TCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGC TGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACA GCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAA ACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 262).

[000559] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 123:

[000560] CAGTCGGTGGAGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGAT CCCTGACACTCACCTGCACAGCCTCTGGATTCGACTTCAGTAGCAATGCAATGT GGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATGCATTTAc AATGGTGATGGCAGCACATACTACGCGAGCTGGGTGAATGGCCGATTCTCCAT CTCCAAAACCTCGTCGACCACGGTGACTCTGCAACTGAATAGTCTGACAGTCG CGGACACGGCCACGTATTATTGTGCGAGAGATCTTGACTTGTGGGGCCCGGGC ACCCTCGTCACCGTCTCGAGC (SEQ ID NO: 263).

[000561] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 124:

[000562] CAGTCGGTGGAGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGAT CCCTGACACTCACCTGCACAGCCTCTGGATTCGACTTCAGTAGCAATGCAATGT GGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATGCATTTAc AATGGTGATGGCAGCACATACTACGCGAGCTGGGTGAATGGCCGATTCTCCAT CTCCAAAACCTCGTCGACCACGGTGACTCTGCAACTGAATAGTCTGACAGTCG CGGACACGGCCACGTATTATTGTGCGAGAGATCTTGACTTGTGGGGCCCGGGC ACCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTG GCAcCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGAC CAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCT CAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCC CAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCC TGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATG ATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGA CCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCA AGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGT CCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGG TCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAA GGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGAT

GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCG
ACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGAC
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGC
ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT
AAATGA (SEQ ID NO: 264).

[000563] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 265; SEQ ID NO: 266; and SEQ ID NO: 267 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 121 or the light chain sequence of SEQ ID NO: 122.

[000564] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 123 or the heavy chain sequence of SEQ ID NO: 124.

[000565] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 261 encoding the light chain variable sequence of SEQ ID NO: 121; the polynucleotide SEQ ID NO: 262 encoding the light chain sequence of SEQ ID NO: 122; the polynucleotide SEQ ID NO: 263 encoding the heavy chain variable sequence of SEQ ID NO: 123; the polynucleotide SEQ ID NO: 264 encoding the heavy chain sequence of SEQ ID NO: 124; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 265; SEQ ID NO: 266; and SEQ ID NO: 267) of the light chain variable sequence of SEQ ID NO: 121 or the light chain sequence of SEQ ID

NO: 122; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 268; SEQ ID NO: 269; and SEQ ID NO: 270) of the heavy chain variable sequence of SEQ ID NO: 123 or the heavy chain sequence of SEQ ID NO: 124.

[000566] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab13, the polynucleotides encoding the full length Ab13 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 262 encoding the light chain sequence of SEQ ID NO: 122 and the polynucleotide SEQ ID NO: 264 encoding the heavy chain sequence of SEQ ID NO: 124.

[000567] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab13 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab13 or Fab fragments thereof may be produced via expression of Ab13 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

Antibody Ab14

[000568] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 131:

[000569] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAATGTTTAcAATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG TAGTCGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 271).

[000570] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 132:

[000571] CAAGTGCTGacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcAATtgcCA GGCCAGTCAGAATGTTTAcAATAACAACTACCTAGCCtggtatcagcagaaaccagggaaagtt cctaagCAActgatctatTCTACATCCACTCTGGCATCTggggtcccatctcgtttcagtggcagtggatctgg gacagatttcactctcaccatcagcagcctgcagcctgaagatgttgcaacttattactgtCTGGGCAGTTATGATTG TAGTCGTGGTGATTGTTTTGTTttcggcggaggaaccaaggtggaaatcaaacgtACGGTGGCTGC ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGC CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGC AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAA AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 272).

[000572] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 133:

[000573] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt ctggaATCGGCCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt cGGAGTCATTGGTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCcg attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat TTCtgtACCAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGC (SEQ ID NO: 273).

[000574] In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 134:

[000575] gaggtgcagctTgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcaGTCt
ctggaATCGGCCTCagtAGCTACTACATGCAAtgggtccgtcaggctccagggaaggggctggagtgggt
cGGAGTCATTGGTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCcg
attcaccatctccagagacaattccaagACCACGGTGtatcttcaaatgaacagcctgagagctgaggacactgctgtgtat
TTCtgtACCAGAGGGGACATCtggggccaagggaccctcgtcaccgtcTCGAGCGCCTCCACCA
AGGGCCCATCGGTCTTCCCCCTGGCAcCCTCCTCCaAGAGCACCTCTGGGGGCA
CAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA
GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC
AAGGTGGACGCGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCC
ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGaTCTCCCgGACCCCTGAGGTCACATGCGTGGT
GGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAG
CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG
GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTT
CTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG
AGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 274).

[000576] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 275; SEQ ID NO: 276; and SEQ ID

NO: 277 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 131 or the light chain sequence of SEQ ID NO: 132.

[000577] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 278; SEQ ID NO: 279; and SEQ ID NO: 280 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 133 or the heavy chain sequence of SEQ ID NO: 134.

[000578] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 271 encoding the light chain variable sequence of SEQ ID NO: 131; the polynucleotide SEQ ID NO: 272 encoding the light chain sequence of SEQ ID NO: 132; the polynucleotide SEQ ID NO: 273 encoding the heavy chain variable sequence of SEQ ID NO: 133; the polynucleotide SEQ ID NO: 274 encoding the heavy chain sequence of SEQ ID NO: 134; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 275; SEQ ID NO: 276; and SEQ ID NO: 277) of the light chain variable sequence of SEQ ID NO: 131 or the light chain sequence of SEQ ID NO: 132; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 278; SEQ ID NO: 279; and SEQ ID NO: 280) of the heavy chain variable sequence of SEQ ID NO: 133 or the heavy chain sequence of SEQ ID NO: 134.

[000579] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab14, the polynucleotides encoding the full length Ab14 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 272 encoding the light chain sequence of SEQ

ID NO: 132 and the polynucleotide SEQ ID NO: 274 encoding the heavy chain sequence of SEQ ID NO: 134.

[000580] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab14 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab14 or Fab fragments thereof may be produced via expression of Ab14 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[000581] In one embodiment, the invention is directed to an isolated polynucleotide comprising a polynucleotide encoding an anti-CGRP VH antibody amino acid sequence selected from SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, or 133, or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-CGRP antibody VH polypeptide or a conservative amino acid substitution.

[000582] In another embodiment, the invention is directed to an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-CGRP VL antibody amino acid sequence of 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, or 131, or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-CGRP antibody VL polypeptide or a conservative amino acid substitution.

[000583] In yet another embodiment, the invention is directed to one or more heterologous polynucleotides comprising a sequence encoding the polypeptides contained in SEQ ID NO:1 and SEQ ID NO:3; SEQ ID NO:11 and SEQ ID NO:13; SEQ ID NO:21 and SEQ ID NO:23; SEQ ID NO:31 and SEQ ID NO:33; SEQ ID NO:41 and SEQ ID NO:43; SEQ ID

NO:51 and SEQ ID NO:53, SEQ ID NO:61 and SEQ ID NO:63; SEQ ID NO:71 and SEQ ID NO:73; SEQ ID NO:81 and SEQ ID NO:83; SEQ ID NO:91 and SEQ ID NO:93; SEQ ID NO:101 and SEQ ID NO:103; SEQ ID NO:111 and SEQ ID NO:113; SEQ ID NO:121 and SEQ ID NO:123; or SEQ ID NO:131 and SEQ ID NO:133.

[000584] In another embodiment, the invention is directed to an isolated polynucleotide that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-CGRP antibody wherein said expressed polypeptide alone specifically binds CGRP or specifically binds CGRP when expressed in association with another polynucleotide sequence that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-CGRP antibody wherein said at least one CDR is selected from those contained in the VL or VH polypeptides of SEQ ID NO: 1, 3, 11, 13, 21, 23, 31, 33, 41, 43, 51, 53, 61, 63, 71, 73, 81, 83, 91, 93, 101, 103, 111, 113, 121, 123, 131, or SEQ ID NO:133.

[000585] Host cells and vectors comprising said polynucleotides are also contemplated.

[000586] The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarity-determining regions (CDRs, or hypervariable regions), as set forth herein, as well as host cells comprising said vector sequences. In one embodiment of the invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus Pichia.

B-cell Screening and Isolation

[000587] In one embodiment, the present invention contemplates the preparation and isolation of a clonal population of antigen-specific B cells that may be used for isolating at least one CGRP antigen-specific cell, which can be used to produce a monoclonal antibody against CGRP, which is specific to a desired CGRP antigen, or a nucleic acid sequence corresponding to such an antibody. Methods of preparing and isolating said clonal population of antigen-specific B cells are taught, for example, in U.S. patent publication no. US 2007/0269868 to Carvalho-Jensen et al., the disclosure of which is herein incorporated by reference in its entirety. Methods of preparing and isolating said clonal

population of antigen-specific B cells are also taught herein in the examples. Methods of "enriching" a cell population by size or density are known in the art. See, e.g., U.S. Patent 5,627,052. These steps can be used in addition to enriching the cell population by antigen-specificity.

Methods of Humanizing Antibodies

[000588] In another embodiment, the present invention contemplates methods for humanizing antibody heavy and light chains. Methods for humanizing antibody heavy and light chains which may be applied to anti-CGRP antibodies are taught, for example, in U.S. patent application publication no. US 2009/0022659 to Olson et al., and in U.S. patent no. 7,935,340 to Garcia-Martinez et al., the disclosures of each of which are herein incorporated by reference in their entireties.

Methods of Producing Antibodies and Fragments thereof

[000589] In another embodiment, the present invention contemplates methods for producing anti-CGRP antibodies and fragments thereof diarrhea. Methods for producing anti-CGRP antibodies and fragments thereof secreted from polyploidal, preferably diploid or tetraploid strains of mating competent yeast are taught, for example, in U.S. patent application publication no. US 2009/0022659 to Olson et al., and in U.S. patent no. 7,935,340 to Garcia-Martinez et al., the disclosures of each of which are herein incorporated by reference in their entireties.

[000590] Other methods of producing antibodies are well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (See, for example, U.S. Patent No. 4,816,567 to Cabilly et al.; Morrison et al., P.N.A.S. USA, 81:8651-55 (1984); Neuberger, M.S. et al., Nature, 314:268-270 (1985); Boulianne, G.L. et al., Nature, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entireties).

[000591] Likewise, other methods of producing humanized antibodies are now well known in the art (See, for example, U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,762, and

6,180,370 to Queen et al; U.S. Patent Nos. 5,225,539 and 6,548,640 to Winter; U.S. Patent Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter et al; U.S. Patent No. 6,632,927 to Adair; Jones, P.T. et al, Nature, 321:522-525 (1986); Reichmann, L., et al, Nature, 332:323-327 (1988); Verhoeyen, M, et al, Science, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

[000592] Antibody polypeptides of the invention having CGRP binding specificity diarrhea may also be produced by constructing, using conventional techniques well known to those of ordinary skill in the art, an expression vector containing an operon and a DNA sequence encoding an antibody heavy chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[000593] A second expression vector is produced using the same conventional means well known to those of ordinary skill in the art, said expression vector containing an operon and a DNA sequence encoding an antibody light chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[000594] The expression vectors are transfected into a host cell by convention techniques well known to those of ordinary skill in the art to produce a transfected host cell, said transfected host cell cultured by conventional techniques well known to those of ordinary skill in the art to produce said antibody polypeptides.

[000595] The host cell may be co-transfected with the two expression vectors described above, the first expression vector containing DNA encoding an operon and a light chain-derived polypeptide and the second vector containing DNA encoding an operon and a heavy chain-derived polypeptide. The two vectors contain different selectable markers, but preferably achieve substantially equal expression of the heavy and light chain polypeptides. Alternatively, a single vector may be used, the vector including DNA encoding both the heavy and light chain polypeptides. The coding sequences for the heavy and light chains may comprise cDNA, genomic DNA, or both.

[000596] The host cells used to express the antibody polypeptides may be either a bacterial cell such as E. coli, or a eukaryotic cell such as P. pastoris. In one embodiment of the invention, a mammalian cell of a well-defined type for this purpose, such as a myeloma cell, a Chinese hamster ovary (CHO) cell line, a NSO cell line, or a HEK293 cell line may be used.

[000597] The general methods by which the vectors may be constructed, transfection methods required to produce the host cell and culturing methods required to produce the antibody polypeptides from said host cells all include conventional techniques. Although preferably the cell line used to produce the antibody is a mammalian cell line, any other suitable cell line, such as a bacterial cell line such as an E. coli-derived bacterial strain, or a yeast cell line, may alternatively be used.

[000598] Similarly, once produced the antibody polypeptides may be purified according to standard procedures in the art, such as for example cross-flow filtration, ammonium sulphate precipitation, affinity column chromatography and the like.

[000599] The antibody polypeptides described herein may also be used for the design and synthesis of either peptide or non-peptide mimetics that would be useful for the same therapeutic applications as the antibody polypeptides of the invention. See, for example, Saragobi et al, Science, 253:792-795 (1991), the contents of which is herein incorporated by reference in its entirety.

Screening Assays

[000600] The invention also includes screening assays designed to assist in the identification of diseases and disorders associated with CGRP and diarrhea in patients exhibiting symptoms of a CGRP associated disease or disorder.

[000601] In one embodiment of the invention, the anti-CGRP antibodies of the invention, or CGRP binding fragments thereof, are used to detect the presence of CGRP in a biological sample obtained from a patient exhibiting symptoms of a disease or disorder associated with CGRP and diarrhea. The presence of CGRP, or elevated levels thereof especially in the colon when compared to pre-disease levels of CGRP in a comparable

biological sample, may be beneficial in diagnosing a disease or disorder associated with CGRP associated with diarrhea.

[000602] Another embodiment of the invention provides a diagnostic or screening assay to assist in diagnosis of diseases or disorders associated with CGRP in patients exhibiting symptoms of a CGRP associated disease or disorder identified herein, comprising assaying the level of CGRP expression in a biological sample from said patient using a post-translationally modified anti-CGRP antibody or binding fragment thereof. The anti-CGRP antibody or binding fragment thereof may be post-translationally modified to include a detectable moiety such as set forth previously in the disclosure.

[000603] The CGRP level in the biological sample is determined using a modified anti-CGRP antibody or binding fragment thereof as set forth herein, and comparing the level of CGRP in the biological sample against a standard level of CGRP (e.g., the level in normal biological samples). The skilled clinician would understand that some variability may exist between normal biological samples, and would take that into consideration when evaluating results. In one embodiment of the invention, the anti-CGRP antibodies of the invention may be used to correlate CGRP expression levels with a particular stage of cancerous development. One skilled in the art would be able to measure CGRP in numerous subjects in order to establish ranges of CGRP expression that correspond to clinically defined stages of cancerous development. These ranges will allow the skilled practitioner to measure CGRP in a subject diagnosed with a cancer and correlate the levels in each subject with a range that corresponds to a stage of said cancer. One skilled in the art would understand that by measuring CGRP in the patient at different intervals, the progression of the cancer can be determined.

[000604] The above-recited assay may also be useful in monitoring a disease or disorder, where the level of CGRP obtained in a biological sample from a patient believed to have a CGRP associated disease or disorder is compared with the level of CGRP in prior biological samples from the same patient, in order to ascertain whether the CGRP level in said patient has changed with, for example, a treatment regimen.

[000605] The invention is also directed to a method of in vivo imaging which detects the presence of cells which express CGRP comprising administering a diagnostically effective

amount of a diagnostic composition. Said in vivo imaging is useful for the detection or imaging of CGRP expressing tumors or metastases, for example, and can be useful as part of a planning regimen for the design of an effective cancer treatment protocol. The treatment protocol may include, for example, one or more of radiation, chemotherapy, cytokine therapy, gene therapy, and antibody therapy, as well as an anti-CGRP antibody or fragment thereof.

[000606] The present invention further provides for a kit for detecting binding of an anti-CGRP antibody of the invention to CGRP. In particular, the kit may be used to detect the presence of a CGRP specifically reactive with an anti-CGRP antibody of the invention or an immunoreactive fragment thereof. The kit may also include an antibody bound to a substrate, a secondary antibody reactive with the antigen and a reagent for detecting a reaction of the secondary antibody with the antigen. Such a kit may be an ELISA kit and can comprise the substrate, primary and secondary antibodies when appropriate, and any other necessary reagents such as detectable moieties, enzyme substrates, and color reagents, for example as described herein. The diagnostic kit may also be in the form of an immunoblot kit. The diagnostic kit may also be in the form of a chemiluminescent kit (Meso Scale Discovery, Gaithersburg, MD). The diagnostic kit may also be a lanthanide-based detection kit (PerkinElmer, San Jose, CA).

[000607] A skilled clinician would understand that a biological sample includes, but is not limited to, sera, plasma, urine, saliva, mucous, pleural fluid, synovial fluid and spinal fluid.

[000608]

[000609] Methods of Ameliorating or Reducing Symptoms of, or Treating, or Preventing, Diseases and Disorders Associated with, CGRP

[000610] The anti-CGRP antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with CGRP especially diarrhea. In a preferred embodiment the anti-CGRP antibodies or antibody fragments will be shown to be efficacious (block adverse side effects associated with excess circulating CGRP including diarrhea in the rodent animal model disclosed in Example 8.

[000611] Anti-CGRP antibodies described herein, or fragments thereof, as well as combinations, can also be administered in a therapeutically effective amount to patients in need of treatment of diseases and disorders associated with CGRP in the form of a pharmaceutical composition as described in greater detail below.

[000612] In another embodiment of the invention, anti-CGRP antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing diarrhea in CGRP related conditions including migraines (with or without aura), weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, pain, hemiplagic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysomal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (such as for example associated with sinusitis), and allergy-induced headaches or migraines.

[000613] In one embodiment of the invention, anti-CGRP antibodies described herein, or fragments thereof and/or with a second agent, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diarrhea associated with the following non-limiting listing of CGRP related diseases and disorders: pain, inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary or metastatic bone cancer pain, fracture pain, chronic pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, abdominal pain, pain associated with sickle cell crises, and other nociceptic pain, as well as hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptic pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, or pain or visceral pain associated with: gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, irritable colon, spastic colon, mucous colitis, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, pancreatitis, renal colic, dysmenorrhea, cystitis, including interstitial cystitis (IC), surgery associated with the ileus, diverticulitis, peritonitis, pericarditis, hepatitis, appendicitis,

colitis, cholecystitis, endometriosis, chronic and/or acute pancreatitis, myocardial infarction, kidney pain, pleural pain, prostatitis, pelvic pain, trauma to an organ, chronic nociceptive pain, chronic neuropathic pain, chronic inflammatory pain, fibromyalgia, breakthrough pain and persistent pain, and cancer pain arising from malignancy or from cancer preferably selected from one or more of: adenocarcinoma in glandular tissue, blastoma in embryonic tissue of organs, carcinoma in epithelial tissue, leukemia in tissues that form blood cells, lymphoma in lymphatic tissue, myeloma in bone marrow, sarcoma in connective or supportive tissue, adrenal cancer, AIDS-related lymphoma, anemia, bladder cancer, bone cancer, brain cancer, breast cancer, carcinoid tumours, cervical cancer, chemotherapy, colon cancer, cytopenia, , endometrial cancer, esophageal cancer, gastric cancer, head cancer, neck cancer, hepatobiliary cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, Hodgkin's disease, lymphoma, non- Hodgkin's, nervous system tumours, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, thyroid cancer, urethral cancer, bone cancer, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells, cancer of bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer, tumours that metastasize to the bone, tumours infiltrating the nerve and hollow viscus, tumours near neural structures. Further preferably the cancer pain comprises visceral pain, preferably visceral pain which arises from pancreatic cancer and/or metastases in the abdomen. Further preferably the cancer pain comprises somatic pain, preferably somatic pain due to one or more of bone cancer, metastasis in the bone, postsurgical pain, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells of the bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer.

[000614] In another embodiment of the invention, anti-CGRP antibodies described herein, or fragments thereof and/or with a second agent, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, the following non-limiting listing of diseases and disorders: cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival.

[000615] In another embodiment of the invention, anti-CGRP antibodies described herein, or fragments thereof and/or with a second agent, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, the following non-limiting listing of diseases and disorders: neurogenic, neuropathic or nociceptic pain. Neuropathic pain may include, but is not limited to, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy and neurogenic pain. In other preferred embodiments, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, and other neuropathic pain.

[000616] In another embodiment of the invention, anti-CGRP antibodies described herein, or fragments thereof and/or with a second agent, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, the following non-limiting listing of diseases and disorders: diarrhea, and visceral pain associated with gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, or pancreatitis.

Administration

[000617] In one embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of between about 0.1 and 100.0 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a recipient subject with a frequency of once every twenty-six weeks or less, such as once every sixteen weeks or less, once every eight weeks or less, once every four weeks or less, once every two weeks or less, once every week or less, or once daily or less.

[000618] Fab fragments may be administered every two weeks or less, every week or less, once daily or less, multiple times per day, and/or every few hours. In one embodiment of the invention, a patient receives Fab fragments of 0.1 mg/kg to 40 mg/kg per day given in divided doses of 1 to 6 times a day, or in a sustained release form, effective to obtain desired results.

[000619] It is to be understood that the concentration of the antibody or Fab administered to a given patient may be greater or lower than the exemplary administration concentrations set forth above in paragraphs [0566] and [0567].

[000620] A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pathophysiologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

[000621] In another embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject in a pharmaceutical formulation.

[000622] A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

[000623] In one embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, may be optionally administered in combination with one or more active agents. Such active agents include analgesic, anti-histamine, antipyretic, anti-inflammatory, antibiotic, antiviral, and anti-cytokine agents. Active agents include agonists, antagonists, and modulators of TNF-α, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-α, IFN-γ, BAFF, CXCL13, IP-10, VEGF, EPO, EGF, HRG, Hepatocyte Growth Factor (HGF), Hepcidin, including antibodies reactive against any of the foregoing, and antibodies reactive against any of their receptors. Active agents also include but are not limited to 2-Arylpropionic acids, Aceclofenac, Acemetacin, Acetylsalicylic acid (Aspirin), Alclofenac, Alminoprofen, Amoxiprin, Ampyrone, Arylalkanoic acids, Azapropazone, Benorylate/Benorilate, Benoxaprofen, Bromfenac, Carprofen, Celecoxib, Choline magnesium salicylate, Clofezone, COX-2 inhibitors, Dexibuprofen, Dexketoprofen, Diclofenac, Diflunisal, Droxicam, Ethenzamide, Etodolac, Etoricoxib, Faislamine, fenamic acids, Fenbufen, Fenoprofen, Flufenamic acid, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuproxam, Indometacin, Indoprofen, Kebuzone, Ketoprofen, Ketorolac, Lornoxicam, Loxoprofen, Lumiracoxib, Magnesium salicylate, Meclofenamic acid, Mefenamic acid, Meloxicam, Metamizole, Methyl salicylate, Mofebutazone, Nabumetone, Naproxen, N-Arylanthranilic acids, Nerve Growth Factor (NGF), Oxametacin, Oxaprozin, Oxicams, Oxyphenbutazone, Parecoxib, Phenazone, Phenylbutazone, Phenylbutazone, Piroxicam, Pirprofen, profens, Proglumetacin, Pyrazolidine derivatives, Rofecoxib, Salicyl salicylate, Salicylamide, Salicylates, Substance P, Sulfinpyrazone, Sulindac, Suprofen, Tenoxicam, Tiaprofenic acid, Tolfenamic acid, Tolmetin, and Valdecoxib.

[000624] An anti-histamine can be any compound that opposes the action of histamine or its release from cells (e.g., mast cells). Anti-histamines include but are not limited to acrivastine, astemizole, azatadine, azelastine, betatastine, brompheniramine, buclizine, cetirizine, cetirizine analogues, chlorpheniramine, clemastine, CS 560, cyproheptadine, desloratadine, dexchlorpheniramine, ebastine, epinastine, fexofenadine, HSR 609, hydroxyzine, levocabastine, loratidine, methscopolamine, mizolastine, norastemizole, phenindamine, promethazine, pyrilamine, terfenadine, and tranilast.

[000625] Antibiotics include but are not limited to Amikacin, Aminoglycosides, Amoxicillin, Ampicillin, Ansamycins, Arsphenamine, Azithromycin, Azlocillin, Aztreonam, Bacitracin, Carbacephem, Carbapenems, Carbenicillin, Cefaclor, Cefadroxil, Cefalexin, Cefalothin, Cefalotin, Cefamandole, Cefazolin, Cefdinir, Cefditoren, Cefepime, Cefixime, Cefoperazone, Cefotaxime, Cefoxitin, Cefpodoxime, Cefprozil, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftobiprole, Ceftriaxone, Cefuroxime, Cephalosporins, Chloramphenicol, Cilastatin, Ciprofloxacin, Clarithromycin, Clindamycin, Cloxacillin, Colistin, Co-trimoxazole, Dalfopristin, Demeclocycline, Dicloxacillin, Dirithromycin, Doripenem, Doxycycline, Enoxacin, Ertapenem, Erythromycin, Ethambutol, Flucloxacillin, Fosfomycin, Furazolidone, Fusidic acid, Gatifloxacin, Geldanamycin, Gentamicin, Glycopeptides, Herbimycin, Imipenem, Isoniazid, Kanamycin, Levofloxacin, Lincomycin, Linezolid, Lomefloxacin, Loracarbef, Macrolides, Mafenide, Meropenem, Meticillin, Metronidazole, Mezlocillin, Minocycline, Monobactams, Moxifloxacin, Mupirocin, Nafcillin, Neomycin, Netilmicin, Nitrofurantoin, Norfloxacin, Ofloxacin, Oxacillin, Oxytetracycline, Paromomycin, Penicillin, Penicillins, Piperacillin, Platensimycin, Polymyxin B, Polypeptides, Prontosil, Pyrazinamide, Quinolones, Quinupristin, Rifampicin, Rifampin, Roxithromycin, Spectinomycin, Streptomycin, Sulfacetamide, Sulfamethizole, Sulfanilimide, Sulfasalazine, Sulfisoxazole, Sulfonamides, Teicoplanin, Telithromycin, Tetracycline, Tetracyclines, Ticarcillin, Tinidazole, Tobramycin, Trimethoprim, Trimethoprim-Sulfamethoxazole, Troleandomycin, Trovafloxacin, and Vancomycin.

[000626] Active agents also include Aldosterone, Beclometasone, Betamethasone, Corticosteroids, Cortisol, Cortisone acetate, Deoxycorticosterone acetate, Dexamethasone, Fludrocortisone acetate, Glucocorticoids, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Steroids, and Triamcinolone. Any suitable combination of these active agents is also contemplated.

[000627] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not

provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

[000628] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[000629] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition. The proper fluidity can be maintained, for example, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[000630] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and

gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[000631] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[000632] The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

[000633] These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

[000634] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the

invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[000635] Certain teachings related to methods for obtaining a clonal population of antigen-specific B cells were disclosed in U.S. Provisional patent application no. 60/801,412, filed May 19, 2006, the disclosure of which is herein incorporated by reference in its entirety.

[000636] Certain teachings related to humanization of rabbit-derived monoclonal antibodies and preferred sequence modifications to maintain antigen binding affinity were disclosed in International Application No. PCT/US2008/064421, corresponding to International Publication No. WO/2008/144757, entitled "Novel Rabbit Antibody Humanization Methods and Humanized Rabbit Antibodies", filed May 21, 2008, the disclosure of which is herein incorporated by reference in its entirety.

[000637] Certain teachings related to producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. Patent application no. 11/429,053, filed May 8, 2006, (U.S. Patent Application Publication No. US2006/0270045), the disclosure of which is herein incorporated by reference in its entirety.

[000638] Certain CGRP antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

[000639] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

[000640] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (e.g. amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is

average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

EXAMPLES

Example 1 *Preparation of Antibodies that Bind CGRP*

[000641] By using the antibody selection protocol described herein, one can generate an extensive panel of antibodies.

Immunization Strategy

[000642] Rabbits were immunized with human CGRP (American Peptides, Sunnyvale CA and Bachem, Torrance CA). Immunization consisted of a first subcutaneous (sc) injection of 100 μg of antigen mixed with 100 μg of KLH in complete Freund's adjuvant (CFA) (Sigma) followed by two boosts, two weeks apart each containing 50 μg antigen mixed with 50 μg in incomplete Freund's adjuvant (IFA) (Sigma). Animals were bled on day 55, and serum titers were determined by ELISA (antigen recognition) and by inhibition of CGRP driven cAMP increase in SK-N-MC.

Antibody Selection Titer Assessment

[000643] To identify and characterize antibodies that bind to human CGRP , antibody-containing solutions were tested by ELISA. Briefly, neutravidin coated plates (Thermo Scientific), were coated with N-term biotinylated human CGRP (50 L per well, 1 g/mL) diluted in ELISA buffer (0.5% fish skin gelatin in PBS pH 7.4,) either for approximately 1hr at room temperature or alternatively overnight at 4°C. The plates were then further blocked with ELISA buffer for one hour at room temperature and washed using wash buffer (PBS,0.05% tween 20). Serum samples tested were serially diluted using ELISA buffer. Fifty microliters of diluted serum samples were transferred onto the wells and incubated for one hour at room temperature for one hour. After this incubation, the plate was washed with wash buffer. For development, an anti-rabbit specific Fc-HRP (1:5000 dilution in ELISA buffer) was added onto the wells and incubated for 45 min at RT. After a 3x wash step with wash solution, the plate was developed using TMB substrate for two minutes at room temperature and the reaction was quenched using 0.5M HCl. The well absorbance was read at 450 nm.

Titer determination of serum samples by functional activity (Inhibition of CGRP driven cAMP levels)

[000644] To identify and characterize antibodies with functional activity, an inhibition of CGRP driven increase of cAMP levels assay was done using electrochemiluminescence (Meso Scale Discovery, MSD). Briefly, antibody preparations to be tested were serially diluted in MSD assay buffer (Hepes, MgCl2, pH 7.3, 1mg/mL blocker A, Meso Scale Discovery) in a 96 well round bottom polystyrene plate (Costar). To this plate, human CGRP was added (10ng/mL final concentration) diluted in MSD assay buffer and incubated for one hour at 37C. Appropriate controls were used as suggested by the assay-kit manufacturer. Human neuroepithelioma cells (SK-N-MC, ATCC) were detached using an EDTA solution (5mM in PBS) and washed using growth media (MEM, 10% FBS, antibiotics) by centrifugation. The cell number was adjusted to 2 million cells per mL in assay buffer, and IBMX (3-Isobutyl-1Methylxanthine, Sigma) was added to a final concentration of 0.2mM right before loading cells onto cAMP assay plate. After the antibody human CGRP solution was incubated for one hour 20 microliters of solution containing cells were transferred to the cAMP assay plate. All tested samples were run in duplicates with appropriate controls. Ten microliters of cells were added to the wells and the plate was incubated for 30 minutes with shaking at room temperature. While cells were being incubated with the CGRP solution, the stop solution was prepared by making a 1:200 solution of TAG labeled cAMP (MSD) in lysis buffer (MSD). To stop the cells-CGRP incubation, 20 microliters of stop solution was added to the cells and the plate was incubated for one hour with shaking at room temperature. The read buffer (MSD) was diluted four times with water and 100 microliters were added to all wells on the plate. The plate was then read using a Sector Imager 2400 (MSD) and the Prism software was used for data fit and IC50 determination.

Tissue Harvesting

[000645] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[000646] Spleen and lymph nodes were processed into a single cell suspension by disassociating the tissue and pushing through sterile wire mesh at 70 μm (Fisher) with a plunger of a 20 cc syringe. Cells were collected in PBS. Cells were washed twice by centrifugation. After the last wash, cell density was determined by trypan blue. Cells were centrifuged at 1500 rpm for 10 minutes; the supernatant was discarded. Cells were resuspended in the appropriate volume of 10% dimethyl sulfoxide (DMSO, Sigma) in FBS (Hyclone) and dispensed at 1 ml/vial. Vials were stored at -70°C in a slow freezing chamber for 24 hours and stored in liquid nitrogen.

[000647] Peripheral blood mononuclear cells (PBMCs) were isolated by mixing whole blood with equal parts of the low glucose medium described above without FBS. 35 ml of the whole blood mixture was carefully layered onto 8 ml of Lympholyte Rabbit (Cedarlane) into a 45 ml conical tube (Corning) and centrifuged 30 minutes at 2500 rpm at room temperature without brakes. After centrifugation, the PBMC layers were carefully removed using a glass Pasteur pipette (VWR), combined, and placed into a clean 50 ml vial. Cells were washed twice with the modified medium described above by centrifugation at 1500 rpm for 10 minutes at room temperature, and cell density was determined by trypan blue staining. After the last wash, cells were resuspended in an appropriate volume of 10% DMSO/FBS medium and frozen as described above.

B cell selection, enrichment and culture conditions

[000648] On the day of setting up B cell culture, PBMC, splenocyte, or lymph node vials were thawed for use. Vials were removed from LN2 tank and placed in a 37°C water bath until thawed. Contents of vials were transferred into 15 ml conical centrifuge tube (Corning) and 10 ml of modified RPMI described above was slowly added to the tube. Cells were centrifuged for 5 minutes at 2K RPM, and the supernatant was discarded. Cells were resuspended in 10 ml of fresh media. Cell density and viability was determined by trypan blue.

a) The following protocol was used for Ab1 and Ab13

[000649] Cells were pre-mixed with the biotinylated human CGRP as follows. Cells were washed again and resuspended at 1E07 cells/80 μL medium. Biotinylated human CGRP was added to the cell suspension at the final concentration of 5 ug/mL and

incubated for 30 minutes at 4°C. Unbound biotinylated human CGRPα was removed performing two 10 ml washes using PBF [Ca/Mg free PBS (Hyclone), 2 mM ethylenediamine tetraacetic acid (EDTA), 0.5% bovine serum albumin (BSA) (Sigma-biotin free)]. After the second wash, cells were resuspended at 1E07 cells/80 µl PBF and 20 µl of MACS® streptavidin beads (Miltenyi Biotech, Auburn CA) per 10E7 cells were added to the cell suspension. Cells and beads were incubated at 4°C for 15 minutes and washed once with 2 ml of PBF per 10E7 cells.

b) The following protocol was used for Ab4, Ab7, Ab9 and Ab11:

[000650] Biotinylated human CGRPα was pre-loaded onto the streptavidin beads as follows. Seventy five microliters of streptavidin beads (Milteny Biotec, Auburn CA) were mixed with N-terminally biotinylated huCGRPα (10ug/ml final concentration) and 300 ul PBF. This mixture was incubated at 4°C for 30 min and unbound biotinylated human CGRPα was removed using a MACS® separation column (Miltenyi Biotec, with a 1ml rinse to remove unbound material. Then material was plunged out, then used to resuspend cells from above in 100ul per 1E7 cells, the mixture was then incubated at 4°C for 30min and washed once with 10 ml of PBF.

[000651] For both a) and b) protocols the following applied: After washing, the cells were resuspended in 500µl of PBF and set aside. A MACS® MS column (Miltenyi Biotec, Auburn CA) was pre-rinsed with 500 ml of PBF on a magnetic stand (Milteni). Cell suspension was applied to the column through a pre-filter, and unbound fraction was collected. The column was washed with 2.5 ml of PBF buffer. The column was removed from the magnet stand and placed onto a clean, sterile 1.5 ml eppendorf tube. 1 ml of PBF buffer was added to the top of the column, and positive selected cells were collected. The yield and viability of positive cell fraction was determined by trypan blue staining. Positive selection yielded an average of 1% of the starting cell concentration.

[000652] A pilot cell screen was established to provide information on seeding levels for the culture. Plates were seeded at 10, 25, 50, 100, or 200 enriched B cells/well. In addition, each well contained 50K cells/well of irradiated EL-4.B5 cells (5,000 Rads) and an appropriate level of activated rabbit T cell supernatant (See U.S. Patent Application

Publication No. 20070269868)(ranging from 1-5% depending on preparation) in high glucose modified RPMI medium at a final volume of 250 µl/well. Cultures were incubated for 5 to 7 days at 37°C in 4% CO2.

B-Cell culture screening by antigen-recognition (ELISA)

[000653] To identify wells producing anti-human CGRPα antibodies, the same protocol as described for titer determination of serum samples by antigen-recognition (ELISA) was used with the following changes. Briefly, neutravidin coated plates were coated with a mixture of both N- and C- terminally biotinylated human CGRPα (50 µL per well, 1µg/mL each). B-cell supernatant samples (50µL) were tested without prior dilution.

Identification of functional activity in B-cell supernatants using CGRP driven cAMP production

[000654] To determine functional activity contained in B-cell supernatants, a similar procedure to that described for the determination of functional titer of serum samples was used with the following modifications. Briefly, B-cell supernatant (20µL) were used in place of the diluted polyclonal serum samples.

Isolation of antigen-specific B-cells

[000655] Plates containing wells of interest were removed from -70 °C, and the cells from each well were recovered using five washes of 200 microliters of medium (10% RPMI complete, 55µM BME) per well. The recovered cells were pelleted by centrifugation and the supernatant was carefully removed. Pelleted cells were resuspended in 100 µl of medium. To identify antibody expressing cells, streptavidin coated magnetic beads (M280 dynabeads, Invitrogen) were coated with a combination of both N- and C- terminal biotinylated human CGRPα . Individual biotinylated human CGRPα lots were optimized by serial dilution. One hundred microliters containing approximately 4x10E7 coated beads were then mixed with the resuspended cells. To this mixture 15 microliters of goat anti-rabbit H&L IgG-FITC (Jackson Immunoresearch) diluted 1:100 in medium were added.

[000656] Twenty microliters of cell/beads/anti-rabbit H&L suspension were removed and 5 microliter droplets were dispensed on a one-well glass slide previously treated with Sigmacote (Sigma) totaling 35 to 40 droplets per slide. An impermeable barrier of paraffin oil (JT Baker) was used to submerge the droplets, and the slide was incubated for 90 minutes at 37°C in a 4% CO2 incubator in the dark.

[000657] Specific B cells that produce antibody can be identified by the fluorescent ring around produced by the antibody secretion, recognition of the bead-associated biotinylated antigen, and subsequent detection by the fluorescent-IgG detection reagent. Once a cell of interest was identified it was recovered via a micromanipulator (Eppendorf). The single cell synthesizing and exporting the antibody was transferred into a microcentrifuge tube, frozen using dry ice and stored at -70°C.

Amplification and sequence determination of Antibody Sequences From Antigen-Specific B Cells

[000658] Antibody sequences were recovered using a combined RT-PCR based method from a single isolated B-cell. Primers containing restriction enzymes were designed to anneal in conserved and constant regions of the target immunoglobulin genes (heavy and light), such as rabbit immunoglobulin sequences, and a two-step nested PCR recovery was used to amplify the antibody sequence. Amplicons from each well were analyzed for recovery and size integrity. The resulting fragments are then digested with AluI to fingerprint the sequence clonality. Identical sequences displayed a common fragmentation pattern in their electrophoretic analysis. The original heavy and light chain amplicon fragments were then digested using the restriction enzyme sites contained within the PCR primers and cloned into an expression vector. Vector containing subcloned DNA fragments were amplified and purified. Sequence of the subcloned heavy and light chains were verified prior to expression.

Recombinant Production of Monoclonal Antibody of Desired Antigen Specificity and/or Functional Properties

[000659] To determine antigen specificity and functional properties of recovered antibodies from specific B-cells, vectors driving the expression of the desired paired heavy and light chain sequences were transfected into HEK-293 cells.

Antigen-recognition of recombinant antibodies by ELISA

[000660] To characterize recombinant expressed antibodies for their ability to bind to human-CGRPα, antibody-containing solutions were tested by ELISA. All incubations were done at room temperature. Briefly, Immulon IV plagtes (Thermo Scientific), were coated with a CGRPα containing solution (1ut/mL in PBS) for 2 hours. CGRPα-coated plates were then washed three times in wash buffer (PBS, 0.05% Tween-20). The plates were then blocked using a blocking solution (PBS, 0.5% fish skin gelatin, 0.05% Tween-20) for approximately one hour. The blocking solution was then removed and the plates were then incubated with a dilution series of the antibody being tested for approximately one hour. At the end of this incubation, the plate was washed three times with wash buffer and further incubated with a secondary antibody containing solution (Peroxidase conjugated affinipure F(ab')2 fragment goat anti-human IgG, Fc fragment specific (Jackson Immunoresearch) for approximately 45 minutes and washed three times. At that point a substrate solution (TMB peroxidase substrate, BioFx) and incubated for 3 to 5 minutes in the dark. The reaction was stopped by addition of a HCl containing solution (0.5M) and the plate was read at 450 nm in a plate-reader.

[000661] Results: Figures 15-18 demonstrate that anti-CGRP antibodies Ab1-Ab14 bind to and recognize CGRPα.

Functional characterization of recombinant antibodies by modulation of CGRP driven intracellular cAMP levels and cross reactivity to rats

[000662] To characterize recombinant expressed antibody for their ability to inhibit CGRPα mediated increased cellular levels of cAMP assay, an electrochemiluminescence assay-kit (Meso Scale Discovery, MSD) was used. Briefly, antibody preparations to be tested were serially diluted in MSD assay buffer (Hepes, MgCl2, pH 7.3, 1mg/mL blocker A ,Meso Scale Discovery) in a 96 well round bottom polystyrene plate (Costar). To this plate, human CGRPα was added (25ng/mL final concentration) diluted in MSD assay

buffer and incubated for one hour at 37°C. Appropriate controls were used as suggested by the assay-kit manufacturer. Human neuroepithelioma cells (SK-N-MC, ATCC) were detached using an EDTA solution (5mM) and washed using growth media (MEM, 10% FBS, antibiotics) by centrifugation. The cell number was adjusted to 2 million cells per mL in assay buffer, and IBMX (3-Isobutyl-1Methylxanthine, 50mM Sigma) was added to a final concentration of 0.2mM right before loading cells onto cAMP assay plate. The antibody human CGRPα solution was incubated for one hour after which 20 microliters of solution containing cells were transferred to the cAMP assay plate. All tested samples were run in duplicates with appropriate controls. Ten microliters of cells were added to the wells and the plate was incubated for 30 minutes with shaking. While cells were being incubated with the CGRP solution, the stop solution was prepared by making a 1:200 solution of TAG labeled cAMP (MSD) in lysis buffer (MSD). To stop the cells-CGRP incubation, 20 microliters of stop solution was added to the cells and the plate was incubated for one hour with shaking. The read buffer (MSD) was diluted four times with water and 100 microliters were added to all wells on the plate. The plate was then read using a Sector Imager 2400 (MSD) and the Prism software was used for data fit and IC50 determination.

[0100] To test for the ability of recombinant antibodies to antagonize human CGRPβ a similar assay was performed with the substitution of the CGRP agonist (CGRPβ 10ng/mL final concentration). Evaluation of the recombinant antibodies to recognize and inhibit rat CGRP-mediated cAMP generation was conducted using rat CGRP (5ng/mL final concentration) and the rat L6 cell line (ATCC).

[000663] Results: Figures 19-37 demonstrate that anti-CGRP antibodies Ab1-Ab14 inhibit CGRPα,.CGRPβ, and rat CGRP mediated increased cellular levels of cAMP.

Example 2: *Enzymatic Production of Fab Fragments*

[000664] Papain digestions were conducted using immobilized papain (Thermo/Pierce) as per manufacturer's instructions. Briefly, purified antibodies were incubated in a cystein/HCl-containing buffer with immobilized papain at 37°C with gentle rocking. The

digestion was monitored by taking an aliquot and analyzing using SDS-PAGE for cleavage of the heavy chain. To stop the reaction, the immobilized papain was spun out and washed using 50 mM Tris pH 7.5 and filtered. Undigested full length antibody and Fc fragments were removed by using a MabSelectSure (GE) column.

Example 3 *Yeast Cell Expression*

Construction of Pichia pastoris expression vectors for heavy and light chain.

[000665] The humanized light and heavy chain fragments were commercially synthesized and subcloned into a pGAP expression vector. The pGAP expression vector uses the GAP promoter to drive expression of the immunoglobulin chain and the human serum albumin (HSA) leader sequence for export. In addition, this vector contains common elements such as a bacterial origin of replication, and a copy of the kanamycin resistance gene which confers resistance to the antibiotic G418 in P. pastoris. G418 provides a means of selection for strains that contain the desired expression vector integrated into their genome.

Transformation of expression vectors into haploid met1 and lys3 host strains of Pichia pastoris

[000666] All methods used for transformation of haploid P. pastoris strains and manipulation of the P. pastoris sexual cycle were done as described in Pichia Protocols (Methods in Molecular Biology Higgings, DR, and Cregg, JM, Eds. 1998. Humana Press, Totowa, NJ). Prior to transformation each vector was linearized within the GAP promoter sequences to direct the integration of the vector into the GAP promoter locus of the P. pastoris genome. Haploid strains were transfected using electroporation and successful transformants were selected on YPDS (yeast extract, peptone dextrose with sorbitol) G418 agar plates. Copy numbers of heavy and light chain genes were determined for haploid strains by Southern blot analysis. Haploid strains were then mated and selected for their ability to grow in the absence of the amino acid markers (i.e., Lys and Met). Resulting diploid clones were then subjected to a final Southern blot to confirm copy numbers of heavy and light chain genes. A clone expressing the antibody of interest was selected using biolayer interferometry Protein-A biosensors to monitor expression (Octet, ForteBio).

Example 4 *Expression of Ab3, Ab6 and Ab14 in Pichia pastoris*

[000667] Three Pichia strains for expression of full-length antibody were made. For all the full length antibody expressing strains, haploids strains were created and subsequently mated. One haploid strain expressed full-length light chain sequence and another haploid strain expressed the full-length heavy chain sequence. Each diploid strain was used to generate a research cell bank and used for expression in a bioreactor.

[000668] First an inoculum was expanded using the research cell bank using medium comprised of the following nutrients (%w/v): yeast extract 3%, anhydrous dextrose 4%, YNB 1.34%, Biotin 0.004% and 100 mM potassium phosphate. To generate the inoculum for the fermenters, the cell bank was expanded for approximately 24 hours in a shaking incubator at 30°C and 300 rpm. A 10% inoculum was then added to Labfors 2.5L working volume vessels containing 1 L sterile growth medium. The growth medium was comprised of the following nutrients: potassium sulfate 18.2 g/L, ammonium phosphate monobasic 36.4 g/L, potassium phosphate dibasic 12.8 g/L, magnesium sulfate heptahydrate 3.72 g/L, sodium citrate dihydrate 10 g/L, glycerol 40 g/L, yeast extract 30 g/L, PTM1 trace metals 4.35 mL/L, and antifoam 204 1.67 mL/L. The PTM1 trace metal solution was comprised of the following components: cupric sulfate pentahydrate 6 g/L, sodium iodide 0.08 g/L, manganese sulfate hydrate 3 g/L, sodium molybdate dihyrate 0.2 g/L, boric acid 0.02 g/L, cobalt chloride 0.5 g/L, zinc chloride 20 g/L, ferrous sulfate heptahydrate 65 g/L, biotin 0.2 g/L, and sulfuric acid 5 mL/L.

[000669] The bioreactor process control parameters were set as follows: Agitation 1000 rpm, airflow 1.35 standard liter per minute, temperature 28°C and pH was controlled at six using ammonium hydroxide. No oxygen supplementation was provided.

[000670] Fermentation cultures were grown for approximately 12 to 16 hours until the initial glycerol was consumed as denoted by a dissolved oxygen spike. The cultures were starved for approximately three hours after the dissolved oxygen spike. After this starvation period, a bolus addition of ethanol was added to the reactor to reach 1% ethanol (w/v). The fermentation cultures were allowed to equilibrate for 15 to 30 minutes. Feed addition was initiated 30 minutes post-ethanol bolus and set at a constant rate of 1 mL/min

for 40 minutes, then the feed pump was controlled by an ethanol sensor keeping the concentration of ethanol at 1% for the remainder of the run using an ethanol sensing probe (Raven Biotech). The feed was comprised of the following components: yeast extract 50 g/L, dextrose 500 g/L, magnesium sulfate heptahydrate 3 g/L, and PTM1 trace metals 12 mL/L. For fermentation of the full length Ab6 and Ab14, sodium citrate dihydrate (0.5g/L) was also added to the feed. The total fermentation time was approximately 90 hours.

Example 5 *Methods of Humanizing Antibodies*

[000671] Methods of humanizing antibodies have been described previously in issued U.S. Patent No. 7935340, the disclosure of which is incorporated herein by reference in its entirety. In some instances, a determination of whether additional rabbit framework residues are required to maintain activity is necessary. In some instances the humanized antibodies still requires some critical rabbit framework residues to be retained to minimize loss of affinity or activity. In these cases, it is necessary to change single or multiple framework amino acids from human germline sequences back to the original rabbit amino acids in order to have desired activity. These changes are determined experimentally to identify which rabbit residues are necessary to preserve affinity and activity. This is now the end of the variable heavy and light chain humanized amino acid sequence.

Example 6 *Inhibition of CGRP Binding to its Cellular Receptor*

[000672] To characterize recombinantly expressed antibodies for their ability to inhibit CGRP binding to its cellular receptor, a radioligand-binding assay was performed as previously described [Elshourbagy et al, Endocrinology 139:1678 (1998); Zimmerman et al, Peptides, 16:421 (1995)]. Membrane preparations of recombinant human CGRP receptors, calcitonin receptor-like receptor and RAMP1 (Chemiscreen, Millipore) were used. Antibody dilutions were preincubated with 125I radiolabeled human CGRPα (0.03nM) for 30 minutes at room temperature. Non-specific binding was estimated in the presence of 0.1uM human CGRPα. Membranes were filtered and washed. The filters were then counted to determine 125I radiolabeled human CGRPα specifically bound.

Results: Figure 38 demonstrates that anti-CGRP antibodies Ab1-Ab13 inhibit CGRP binding to its cellular receptor.

Example 7 *Inhibition of Neurogenic Vasodilation by Anti-CGRP Antibodies in Rats*

[000673] CGRP is a potent vasodilator (Nature 313: 54-56 (1985) and Br J. Clin. Pharmacol. 26(6):691-5. (1988)). A pharmacodynamic assay to measure CGRP receptor antagonist activity non-invasively was used to characterize anti-CGRP antibodies. The model relied on changes in dermal blood flow measured using a laser Doppler imaging following the topical application of a capsaicin solution. Capsaicin activates the transient receptor potential vanilloid type 1 receptor (TRPV-1), producing neurogenic inflammation and vasodilatation via the local release of vasoactive mediators including CGRP and substance P (Br. J. Pharmacol. 110: 772-776 (1993)).

[000674] On the day prior to the vasodilatation assay, animals were dosed with the test agent or control via IP (intraperitoneal). Following dosing, the animals were shaved and depilated in the lower back region of their dorsal side, in an area approximately 2x6cm. The animals were then returned to their cages overnight. On the day of test, approximately 24 hours post dosing, animals were anesthetized with isoflurane gas and placed on a temperature controlled heating pad and fitted with a nose cone for continuous delivery of isoflurane. A laser doppler imager was used for the observation of vasodilatation. A beam of coherent red light generated by a 633 nm helium-neon laser was directed to the shaved area, a rectangle (2x6 cm), and scanned at a medium resolution mode. A baseline Doppler scan was obtained first and the location of O-ring placement predetermined by identifying two similar low flux areas. Two rubber Orings (~1cm in diameter) were placed in the selected regions and a baseline scan was performed. Immediately after completion of the scan, 1mg of capsaicin in 5 μL of an ethanol:acetone solution (1:1) was applied within each of the two O-rings Doppler scans were repeated at 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5 and 30 minutes after the application of capsaicin. Percent change from baseline mean Flux within each of the two O-rings, was plotted as the results of vasodilatation due to capsaicin.

[000675] In order to test recombinantly expressed antibodies for their ability to inhibit CGRP binding to its cellular receptor, a radioligand-binding assay was performed as previously described.

[000676] Results: Figures 39 and 40 demonstrates that anti-CGRP antibodies Ab3 and Ab6 reduced vasodilation in this model following capsaicin administration.

Example 8 Use of Anti-CGRP Antibodies to Block CGRP Induced Diarrhea in Two Strains of Mice (Nestin/ human RAMP1 Transgenic Mice and C57BL/6J Mice)

[000677] The initial discovery that CGRP antibodies can be used to prevent or treat CGRP induced diarrhea was based on studies on the effect of CGRP antibodies on CGRP induced photophobia or photoaversion. This was effected as one of the hallmarks of migraines is photophobia, or increased sensitivity to light [Mulleners et al, Headache 41: 31-39 (2001); Recober et al, J. Neuroscience 29:8798:8804 (2009)]. It is also known that migraineurs, but not non-migraineurs, are sensitive to CGRP-induced headache [reviewed in Neurology 22:241-246 (2009)]. CGRP binds to a G protein coupled receptor called CLR (calcitonin like receptor) that works concomitantly with the receptor activity modifying protein 1 (RAMP1) in mediating CGRP binding and signaling. In vitro, the activity of CGRP is strongly enhanced by overexpression of the RAMP1 subunit of the CGRP receptor [(J. Neurosci. 27:2693-2703 (2007)]. To study light aversion behavior in mice, a nestin/human-RAMP1 transgenic mouse model was developed [Recober et al, J. Neuroscience 29: 8798-8804 (2009); Russo et al, Mol. Cell. Pharmacol., 1:264-270 (2009)]. These mice when exposed to CGRP present symptoms associated with migraines in particular light aversion (ibid). This protocol is detailed below.

LIGHT AVERSION PROTOCOL

[000678] To test the ability of anti-CGRP antibodies to block CGRP-induced photophobia, mice are housed under standard conditions in groups of 2-5 per cage with a 12 hour light cycle (lights on at 0500 CST)/0600 CDT and off at 1700 CST/1800 CDT) and access to water and food ad libitum. The mice used in the studies are comprised in mice colonies of genotype Nestin/hRAMP1 that contain two transgene alleles Tg(Nes-cre)1Kln/J and Tg(RAMP1) alleles (B6;SJL-Tg(Nes-cre)1Kln Tg(RAMP1). Nes-cre was introduced in these mice by an intercross involving mice obtained from The Jackson Laboratory (stock 003771) on a B6 genetic background.

[000679] The control mice used in the protocol are littermates that are either non-transgenic, or single transgenic (not expressing hRAMP1) containing either transgene: nestin- cre or Cx1-GFP-hRAMP1. The stock colony is maintained by backcrossing CX1-GFP-hRAMP1 mice with non-transgenic littermates in the barrier facility. For behavior studies, the colony is maintained by crossing CX1-GFP-hRAMP1 single transgenic with nestin-cre mice in non-barrier facilities. All of these mice are cared for by animal care and procedures approved by the University of Iowa Animal Care and Use Committee and further are performed in accordance with the standard set by the National Institutes of Health.

[000680] The materials and equipment used in this protocol include a Light/Dark Box and testing chambers comprising a plexiglass open field (27 x 27 x 20.3 cm) containing 16 beam infrared arrays (Med Associates Inc., St. Albans, VT). The light/dark box is divided in two equally sized zones by a dark insert that is opaque to visible light. There is a opening (5.2 x 6.8 cm) in the dark insert that allows the mouse to freely move between the two zones. This testing chamber is placed inside a sound-attenuating cubicle (56 x 38 x 36 cm) with a fan for ventilation (Med Associates Inc.). There are six chambers for the overall system that integrates with a computer containing software for recording and data collection (Med Associates Inc.).

[000681] The software used to monitor results are Activity Monitor v 6.02 (Med Associates Inc.). The software settings used for recording comprise: Resolution (ms): 50, Box Size: 3, Resting Delay (ms): 500, Ambulatory Trigger: 3, Session Type: C, Session Time (min): 20, Block Interval (sec): 300, and Compressed File: DEFAULT.ZIP.

[000682] In the protocol the light source for each chamber is an LED panel which is was installed to the ceiling of the sound-attenuating cubicle. The LED panel contains 36 collimated – 1 watt LED bulbs (5500k Daylight White) (LEDwholesalers, Burlingame, CA). To control light intensity, each LED panel is connected to a dimmable LED driver (LINEARdrive; eldoLED America Inc., San Jose, CA) leading to a potential range of light intensity from ~300 to 27,000 lux. The standard light intensity is ~1000-1200 lux unless otherwise stated.

[000683] The injectors used are hand-made by inserting a stripped 30 gauge x ½" needle into non-radiopaque polyethylene tubing (inner diameter .38 mm; outer diameter 1.09 mm). Using the tubing described above, a stopper (~1cm in length) is placed over the needle leaving approximately 2.5 mm of the bevel uncovered. These injectors are connected to a 10 μL Hamilton syringe.

[000684] The mice are injected ICV with rat α-CGRP (Sigma) diluted in Dulbecco phosphate-buffered saline (D-PBS) (Hyclone). The total dose delivery is 0.5 nmol. For example, 250 or 500 μg CGRP is diluted in 250 or 500 μL sterile PBS for a final concentration of 1 μg/μL. The CGRP is stored at-20°C and aliquots are freeze-thawed at most one time. The PBS is stored at 4°C.

[000685] The mice are administered an exemplary anti-CGRP antibody disclosed herein (Ab3) which is stored at 4°C prior to administration. In this protocol prior to the administration of the antibody i.e., approximately 24 hours prior to testing, the mice are weighed and then receive a systemic (intraperitoneal (ip)) injection of either: vehicle, control antibody (anti-digoxin antibody), or CGRP-binding antibody at a dosage of 30 mg/kg. The mice are also screened to detect any abnormal physical conditions that could affect the assay such as a missing eye, cataracts, or other abnormalities such as grooming, etc. The day after antibody administration, mice are transported in cages from animal housing on a cart and then the mice are placed in the behavior room for acclimation at least 1 hour prior to any injection or testing. Any coverings required for transport are removed from the cages and normal light conditions (standard overhead fluorescent lighting) are turned on during acclimation and remain on for the remainder of the procedure. In addition, all equipment that produces sound including anesthetic devices, light/dark chambers, and LED panels are turned on during acclimation and remain until testing is complete. Typically there is minimal human presence in the room during acclimation.

[000686] After acclimation each mouse is placed in an induction chamber and administered 3.5% isoflurane. After the mouse is anesthetized, it is transferred to a nose cone maintaining 3.5% isoflurane administration, so that it remains anesthetized during injection. Thereafter drug administration is effected using the injector by direct injection

into the right lateral ventricle through the intact scalp aiming at 1 mm posterior to bregma and 1 mm right from the midline.

[000687] Typically for consistency all the injections are performed by the same person after a period of training yielding a success rate of >90% as demonstrated by injections of dye into the ventricles. The drugs injected are either 2.0 μL vehicle (D-PBS) μL or 2.0 μg CGRP in 2.0 μL vehicle (1 μg/μL) administered as a direct intracerebroventricular injection into the right lateral ventricle of the brain through the intact scalp aiming at 1 mm posterior to bregma and 1 mm right from the midline as described before [Recober et al, J. Neuroscience 29: 8798-8804 (2009)] After all 2.0 μL is delivered, the needle remains in place for 10 sec and then removed. The time of injection is then recorded.

[000688] After injection the mice are allowed to recover for 30 minutes prior to testing in an empty, uncovered cage containing a paper towel for bedding. During recovery, the following is recorded: diarrhea, excessive urination, bleeding post-injection, abnormal behavior such as lack of movement, seizures, etc. Based on these observations it is determined whether the administration of the anti-CGRP antibody has an effect (preventative or palliative) on CGRP-induced diarrhea in the transgenic mice which are administered antibody and later administered CGRP ICV relative to the transgenic mice which are only administered CGRP and the control (vehicle or control antibody in vehicle). Antibodies which inhibit CGRP induced diarrhea in this protocol are identified as being potentially useful in treating or preventing acute or chronic diarrhea, particularly diarrhea that is associated with elevated CGRP levels.

[000689] After a 30 minute recovery the light protocol testing is effected. Each mouse is placed along the back wall (furthest from the opening between the two zones) in the light zone approximately in the center. This triggers the recording to begin. Up to six mice are tested at one time (one mouse per chamber). During testing the shelf with the chamber is pushed back into the cabinet and the doors closed. The software records mouse movement for 20 minutes. After the recording is completed, each mouse is removed and placed back in home cage for transport back to animal housing.

[000690] ***Results***

[000691] Using this protocol an anti-CGRP antibody developed by Alder Biopharmaceuticals identified as Ab3 herein was demonstrated to result in the transgenic mice spending a statistically significant amount of time in the light. (These results are not shown as they relate to a different invention which is disclosed in U.S. Provisional Application No. 61/496,860 (Atty. Docket No. 67858.760000) filed June 14, 2011 and U.S. Ser. No. _____ (Attorney Docket No. 67858.730303) filed on even date as this application, and which application is incorporated by reference herein).

[000692] Of relevance to the present invention it was discovered during these experiments that the mice which were treated with the same Alder anti-CGRP antibody (Ab3) also did not exhibit CGRP-associated diarrhea. Whereas CGRP administration elicited diarrhea in the majority of the transgenic mice used in the photoaversion studies which were not administered the anti-CGRP antibody, diarrhea was not observed in the same transgenic mice who received the CGRP administration and which further were administered Ab3 systemically (intraperitoneally).

[000693] These results are shown in Figure 41. More specifically, Figure 41 contains the results of experiments wherein the effects of intracerebroventricular (ICV) injected CGRP in transgenic Nestin/hRamp1 mice. The data show that ICV injected rat CGRP induced diarrhea in Nestin/hRAMP1 tg mice and that the intraperitoneal injection of Ab3 (30mgs/kg, ~24 hrs. prior to CGRP challenge) inhibits intra cerebroventricular (ICV) injected-CGRP induced diarrhea in nestin/hRAMP1 tg mice.

[000694] It can be seen from the figure that all of the transgenic Nestin/hRamp1 mice which did not receive the CGRP (mice administered IP vehicle and ICV vehicle only) did not develop diarrhea. In these studies the RAMP1 transgenic C57/BL6J mice received rat CGRP(alpha).

[000695] By contrast, the majority of the same transgenic mice which received rat CGRP administered ICV and which further were administered controls (either the control antibody in the IP vehicle or a combination of the IP and ICV vehicle) developed diarrhea (was respectively observed in 90% or about 80% of the mice which received the CGRP and the antibody or vehicle controls) Most significantly the data in Figure 41 shows that all of

transgenic mice which received the Alder Ab3 antibody and CGRP did not develop diarrhea.

[000696] In addition, experiments were conducted in non-transgenic mice (C57BL/6J mice). In contrast to the prior studies using the Nestin/hRAMP1 mice, the C57/BL6J strain were administered human CGRP(α) These experiments resulted in similar results, i.e., the anti-CGRP antibody prevented CGRP-associated diarrhea in these animals. These results cumulatively suggest that antibodies which specifically bind CGRP (and likely other polypeptides that inhibit the CGRP/CGRP receptor interaction) may be used to inhibit CGRP associated diarrhea in different individuals, and treat different conditions or treatments involving excess CGRP levels such as those identified herein.

[000697] Figures 42-44 contain the results of these similar CGRP experiments effected in non-transgenic (C57BL/6J mice). These results show that the same anti-CGRP antibody (Ab3) prevented diarrhea in the C57BL/6J mice which received human CGRP. By contrast the majority of the C57BL/6J mice which received the human CGRP(α) and the same controls developed diarrhea.

[000698] Specifically, Figure 42 contains the results of experiments which show that the intra cerebroventricular (ICV) injection of human CGRP (similar to rat CGRP) induces diarrhea in a dose dependent manner in C57BL/6J mice. The data also shows that about 80% of the C57BL/6J mice administered 2.0 μg of human CGRP via intra cerebroventricular injection developed diarrhea whereas none of the mice who received the control or a reduced amount of human CGRP (0.4 μg) developed diarrhea.

[000699] Figure 43 contains the results of additional experiments which show that intra peritoneal injection of Ab3 (30mgs/kg ip, ~24 hrs. prior to CGRP challenge) inhibits ICV injected-CGRP induced diarrhea in C57/BL6J mice. By contrast the administration of the control antibody or vehicle had no effect on ICV injected CGRP-induced diarrhea.

[000700] Figure 44 contains the results of additional experiments which show that Ab3 (30mgs/kg ip injection ~24 hrs. prior to human CGRP challenge) inhibits IP injected-CGRP induced diarrhea in C57/BL6J mice. By contrast the administration of the control antibody contained in the same vehicle as Ab3 had no effect on CGRP-induced diarrhea.

[000701] These results obtained in different strains of mice persuasively demonstrate that the administration of an anti-CGRP antibody or antibody fragment may prevent or ameliorate diarrhea, especially in conditions which are associated with elevated CGRP levels. These results further indicate that there is a similar prophylactic effect when the CGRP is administered by 2 different means (intraperitoneal or intracerebroventricular injection) and is specific to different species. Accordingly the anti-CGRP antibody is apparently able to effectively bind the CGRP and prevent its adverse diarrhea effects irrespective of whether it was delivered systemically or locally via ICV injection.

[000702] In addition, the results show that assays in rodents which are administered CGRP may be used to assess whether a candidate anti-CGRP antibody or another CGRP/CGRP receptor polypeptide inhibitor may be used to inhibit or treat gastrointestinal disorders or other conditions characterized by excessive CGRP that involve aberrations in bowel movements, electrolyte balance and/or fluid excretion, and in particular diarrhea. These conditions include by way of example inflammatory bowel disease, bacterial or viral induced diarrhea. functional bowel disorders selected from the group consisting of gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, diverticulosis, and diverticulitis, Crohn's disease, ileitis, collagenous colitis, lymphocytic colitis, and ulcerative colitis and cancers and cancer treatments associated with diarrhea, e.g., medullary thyroid carcinoma or colorectal cancer and other conditions previously identified.

Example 9 *Effect of CGRP Antibody Administration on Colonic Evacuation*

[000703] Experiments were conducted in C57BL/6 mice to assess the potential efficacy of CGRP antibody administration for the treatment or prevention of diarrhea and related gastrointestinal disorders. Relative to the experiments using C57BL/6J mice in Example 8, a higher dosage of CGRP and a lower dosage of antibody was utilized; nonetheless, Ab3 and Ab6 were effective in decreasing the incidence of diarrhea.

[000704] *Methods*

[000705] Male C57BL/6 mice (Harlan Laboratories) at 6-8 weeks of age were housed individually in clear polycarbonate conventional cages or clear/yellow polycarbonate microisolator cages with certified irradiated contact bedding and acclimated to the study

facility for at least 24 hours. Food and water were given *ad libitum*. Environmental controls were set to maintain temperatures of 18 to 26 degrees C (64 to 79 degrees F) with a relative humidity of 30% to 70%. A 12:12 hour light:dark cycle was maintained.

[000706] Animals were randomized into four treatment groups (ten animals each), based on body weight on the day following arrival. The mean body weights for each group was reviewed to ensure that the mean values and standard deviation satisfied the assumption of homogeneity.

[000707] On day 1, treatment groups 1 and 2 were administered the negative control antibody (of the same isotype as the anti-CGRP antibodies) and groups 3 and 4 received antibodies Ab3 and Ab6, respectively (all antibodies administered i.p. at 10 mg/kg, dose volume 2.63 mL/kg).

[000708] On day 2, treatment groups 2, 3, and 4 were administered CGRP (0.05 mg/kg, dose volume 3.33 mL/kg) i.p. and group 1 was administered an equal dose volume of phosphate buffered saline i.p.. The animals were then placed on a piece of absorbent paper inside a cage separate from their home cage immediately post dose. The piece of paper was weighed prior to placing it in the bottom of the cage and the weight was recorded. Each animal's bowel movements were monitored for 30 minutes post CGRP dose. Observations were made as incidence and total weight of diarrhea (that which sticks to the paper). A positive incidence of diarrhea was recorded if a loose stool was present. Gross fecal weight was determined by lifting the paper out of the cage by grasping the long side and lifting while holding the paper at approximately a 45 degree angle, and shaking lightly. Any stools that rolled off were considered normal, anything that stuck to the paper was considered diarrhea. The piece of paper with any stools attached was then placed on the scale and weighed.

[000709] *Results*

[000710] After CGRP administration the effects of the two different anti-CGRP antibodies on gastrointestinal distress, in this case diarrhea, were assessed during a 30 minute observation period and compared with the two control groups. As shown in FIG. 45, 80% of the positive control animals (receiving CGRP and the negative control antibody) exhibited diarrhea, compared to only 60% and 40% of the animals receiving Ab6 and Ab3.

None of the negative control animals exhibited diarrhea. In addition, the gross fecal weight in the animals which received the CGRP antibody was significantly less than the control animals (FIG. 46). Further, the fecal consistency in the animals which received the control antibody was much more fluid (watery) relative to the animals which received the anti-CGRP antibodies, another indication that the CGRP antibody had helped to restore normal gastrointestinal function and specifically normal colonic evacuation.

[000711] These results further confirm that an anti-CGRP antibody may be effective to prevent or treat diarrhea and related conditions.

Example 10 *Effect of CGRP Antibody Administration on Colonic Evacuation*

[000712] A further experiment was conducted in C57BL/6 mice to assess the potential efficacy of CGRP antibody administration for the treatment or prevention of diarrhea and related gastrointestinal disorders. A higher dosage of anti-CGRP antibodies was utilized than in Example 9 and the effect on diarrhea incidence and gross fecal weight was more pronounced.

[000713] *Methods*

[000714] Diarrhea was experimentally induced in C57BL/6 mice, with ten mice in each of four treatment groups as in Example 9, except that the dosage of each antibody was three times higher (30 mg/kg, dose volume 7.89 mL/kg), and the dose volume of CGRP was three times higher though the dosage of CGRP was the same (0.05 mg/kg, dose volume was 10 mL/kg). Group 1 (negative control) received the negative control antibody on day 1 and phosphate buffered saline on day 2. Groups 2, 3, and 4 received the control antibody, Ab3, and Ab6, respectively, on day 1, and CGRP on day 2. Antibodies and CGRP were administered i.p..

[000715] *Results*

[000716] After CGRP administration the effects of the two different anti-CGRP antibodies on gastrointestinal distress, in this case diarrhea, was assessed during a 30 minute observation period and compared with the two control groups. As shown in FIG. 47, 80% of the positive control animals (receiving CGRP and the negative control antibody) exhibited diarrhea, compared to only 40% and 20% of the animals receiving Ab6 and Ab3.

None of the negative control animals exhibited diarrhea. In addition, the average gross fecal weight in the animals which received the anti-CGRP antibodies was significantly less than the control animals (FIG. 48). Further, the fecal consistency in the animals which received the control antibody was much more fluid (watery) relative to the animals which received the anti-CGRP antibodies, another indication that the CGRP antibody had helped to restore normal gastrointestinal function and specifically normal colonic evacuation.

[000717] These results further confirm that an anti-CGRP antibody may be effective to prevent or treat diarrhea and related conditions.

CLAIMS

What is claimed is:

1). A method of inhibiting, preventing or treating diarrhea or dysentery and/or maintaining appropriate electrolyte and fluid levels in the colon of a subject having a condition associated with diarrhea or dysentery comprising administering an effective amount of an anti-CGRP antibody or anti-CGRP antibody fragment or an anti-CGRP receptor antibody or antibody fragment.

2) The method of Claim 1, wherein the diarrhea or dysentery is associated with increased CGRP.

3). The method of claim 1 or 2, wherein the diarrhea is acute diarrhea or chronic diarrhea.

4) The method of claim 1 or 2, wherein the diarrhea comprises osmotic diarrhea, secretory diarrhea, motility diarrhea, exudative diarrhea, and/or inflammatory diarrhea.

5). The method of claim 1 or 2, wherein diarrhea is caused by a chronic or acute condition selected from a functional bowel disorder, irritable bowel syndrome, coeliac disease, pancreatic disease, pancreatitis, type 1 or type 2 diabetes, cystic fibrosis, Crohn's disease, diabetic neuropathy, menstruation, hyperthyroidism, hormone imbalance, enteritis, an inflammatory bowel disease, microscopic colitis, ischemic bowel disease, ulcerative colitis, mucositis, or tuberculosis.

6). The method of claim 1 or 2, wherein the condition associated with diarrhea is a bacterial, parasitic or viral induced diarrhea.

7) The method of claim 1 or 2, wherein the condition resulting in diarrhea is a parasite selected from Entaamoeba histolytica, Giardia, or another protozoan.

8) The method of claim 1 or 2,, wherein the condition resulting in diarrhea is a bacterium selected from E coli, Shigella, Entaamoeba histolytica, Salmonella, Campylobacter, or Clostridium difficile.

9) The method of claim 1 or 2, wherein the condition resulting in diarrhea is a virus selected from rotavirus, RSV, HIV, norvovirus, adenovirus, and astrovirus.

10) The method of claim 1 or 2, wherein the condition resulting in diarrhea is food poisoning.

11). The method of claim 1 or 2, wherein the condition associated with diarrhea is a functional bowel disorder selected from the group consisting of gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, bile acid malabsorption, and diverticulitis.

12). The method according to claim 1 or 2, wherein the associated with diarrhea is an inflammatory bowel disease is selected from the group consisting of Crohn's disease, ileitis, collagenous colitis, lymphocytic colitis, and ulcerative colitis.

13). The method of claim 1 or 2, wherein the condition associated with diarrhea is a cancer or a cancer treatment associated with diarrhea.

14). The method of claim 13 wherein the cancer is medullary thyroid carcinoma, hormone secreting tumor condition, renal cancer, liver cancer, or a colorectal cancer.

15). The method of claim 13 wherein the cancer treatment associated with diarrhea is selected from chemotherapy, cytokine therapy and radiation or a combination thereof.

16) The method of claim 13 or 15, wherein said treatment results in mucositis or damage to the intestinal brush border.

17). The method of claim 15, wherein the chemotherapy includes a platinum compound.

18). The method of claim 1 or 2, wherein the condition associated with diarrhea is a drug, chemotherapy, an immunoregimen, cell therapy, and/or radiation therapy.

19). The method of Claim 18, wherein the drug associated with diarrhea is an antibiotic, analgesic agent such as an NSAID or opioid compound, antidepressant, or hormone.

20). The method of claim 1 or 2, wherein the antibody or antibody fragment is administered as a monotherapy.

21). The method of claim 1 or 2, wherein the antibody or antibody fragment is administered with another anti-diarrhea treatment agent.

22) The method of claim 21, wherein the other agent is an anti-motility agent such as loperamide, a bismuth compound, codeine, zinc compound, bile acid sequestrant such as cholestryamine, colestipol, or colesevelam, electrolyte solution or probiotic.

23). The method of any one of claims 1-22 wherein the antibody or antibody fragment is an anti-human CGRP antibody or antibody fragment which specifically binds to the same or an overlapping linear or conformational epitope(s) and/or competes for binding to the same or an overlapping linear or conformational epitope(s) on an intact CGRP polypeptide or fragment thereof as an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

24). The method of any one of claims 1-23 wherein the antibody or antibody fragment specifically binds to the same or an overlapping linear or conformational epitope(s) and/or competes for binding to the same or an overlapping linear or conformational epitope(s) on an intact human CGRP polypeptide or a fragment thereof as Ab3, Ab6, Ab13 or Ab14.

25). The method of any one of claims 1-24 wherein the antibody fragment is selected from a Fab fragment, a Fab' fragment, or a F(ab')2 fragment.

26). The method of claim 25, wherein said fragment is a Fab fragment.

27) The method of any one of claims 1-26, wherein said anti-human CGRP antibody or antibody fragment comprises 1, 2, 3, 4, 5 or all 6 CDRs identical to those contained in an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

28) The method of claim 27, wherein at least 2 of the CDRs are identical to those contained in an antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

29) The method of claim 27, wherein at least 3 of the CDRs are identical to those contained in an antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

30) The method of claim 27, wherein at least 4 of the CDRs are identical to those contained in an antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

31) The method of claim 27, wherein at least 5 of the CDRs are identical to those contained in an antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

32) The method of claim 27, wherein all 6 of the CDRs are identical to those contained in an antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

33). The method of any one of claims 1-32 wherein the antibody or antibody fragment comprises a variable light chain comprising the CDR 1 sequence of SEQ ID NO:25, the CDR 2 sequence of SEQ ID NO:26, and the CDR 3 sequence of SEQ ID NO:27, and/or a variable heavy chain comprising the CDR 1 sequence of SEQ ID NO:28, the CDR 2 sequence of SEQ ID NO:29, and the CDR 3 sequence of SEQ ID NO:30.

34). The method of any one of claims 1-32 wherein the antibody or antibody fragment comprises a variable light chain comprising the CDR 1 sequence of SEQ ID NO:55, the CDR 2 sequence of SEQ ID NO:56, and the CDR 3 sequence of SEQ ID NO:57, and/or a variable heavy chain comprising the CDR 1 sequence of SEQ ID NO:58, the CDR 2 sequence of SEQ ID NO:59, and the CDR 3 sequence of SEQ ID NO:60.

35). The method of any one of claims 1-32 wherein the antibody or antibody fragment comprises at least 2 complementarity determining regions (CDRs) in each of the variable light and the variable heavy regions which are identical to those contained in an anti-human CGRP antibody selected from Ab2, Ab3, Ab4, Ab5, or Ab6, Ab13 or Ab14

36). The method of any one of claims 1-32 wherein the antibody or antibody fragment comprises at least 3, 4, 5 or 6 complementarity determining regions (CDRs) in each of the variable light and the variable heavy regions which are identical to those contained in Ab3, Ab6, Ab13 or Ab14.

37). The method of any one of claims 1-36 wherein the antibody or antibody fragment is non-glycosylated or lacks N-glycosylation or if glycosylated only contains only mannose residues.

38). The method of any one of claims 1-37 wherein the antibody or antibody fragment contains an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation.

39). The method of any one of claims 1-38 wherein the antibody or antibody fragment is a humanized, single chain or chimeric antibody.

40). The method of any one of claims 1-39 wherein the antibody or antibody fragment specifically binds to CGRP expressing human cells and/or to circulating soluble CGRP molecules *in vivo*.

41). The method of any one of claims 1-40 wherein the antibody or antibody fragment comprises a V_H polypeptide sequence selected from: SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, or 133, or a variant thereof at least 90% identical thereto; and further comprising a V_L polypeptide sequence selected from: SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121 or 131, or a variant thereof at least 90% identical thereto, wherein one or more of the framework (FR) or CDR residues in said V_H or V_L polypeptide has been substituted with another amino acid residue resulting in an anti-CGRP antibody that specifically binds CGRP.

42). The method of claim 41 wherein one or more of said FR residues are substituted with an amino acid present at the corresponding site in a parent rabbit anti-CGRP antibody from which the complementarity determining regions (CDRs) contained in said V_H or V_L polypeptides have been derived or by a conservative amino acid substitution.

43). The method of any one of Claims 1-42, wherein said antibody or antibody fragment is humanized.

44). The method of any one of Claims 1-42, wherein said antibody or antibody fragment is chimeric.

45). The method of any one of Claims 1-39, wherein said antibody or antibody fragment comprises a single chain antibody.

46.). The method of claim 44, wherein said chimeric antibody comprises a human F_c.

47). The method of claim 46, wherein said human F_c is derived from IgG1, IgG2, IgG3, or IgG4.

48). The method of any one of claims 1-47 wherein the antibody or antibody fragment inhibits the association of CGRP with CGRP-R and/or multimers thereof, one or more additional proteins in a CGRP-CGRP-R complex, and/or antagonizes the biological effects thereof.

49). The method of claim 41 wherein the antibody or antibody fragment comprises a polypeptide sequence having at least 90% or greater homology to any one of the polypeptide sequences recited therein.

50). The method of claim 41 wherein the antibody or antibody fragment comprises a polypeptide sequence having at least 95% or greater homology to any one of the polypeptide sequences recited therein.

51). The method of any one of Claims 1-50, wherein the CGRP antibody or antibody fragment binds to CGRP with an off-rate (K_{off}) of less than or equal to 10^{-4} S^{-1}, $5x10^{-5}$ S^{-1}, 10^{-5} S^{-1}, $5x10^{-6}$ S^{-1}, 10^{-6} S^{-1}, $5x10^{-7}$ S^{-1}, or 10^{-7} S^{-1}.

52). The method of any one of Claims 1-51 wherein the antibody or antibody fragment inhibits the production of CGRP with CGRP-R and/or multimers thereof, and the production of CGRP with CGRP-R and one or more additional proteins in a complex.

53). The method of any one of claims 1-52 wherein the anti-CGRP antibody or antibody fragment binds to the same or an overlapping CGRP epitope as an anti-CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13 or Ab14.

54). The method of any one of claims 1-53 wherein the anti-CGRP antibody or antibody fragment comprises one or more of the CDRs contained in the V_H polypeptide sequences selected from: SEQ ID NO: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, or 133 and/or one or more of the CDRs contained in the V_L polypeptide sequences selected from: SEQ ID NO: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121 or 131.

55). The method of any one of claims 1-54 wherein the antibody or antibody fragment is administered intramuscularly, subcutaneously, intravenously, rectally, by infusion, orally, transdermally or via inhalation.

56). The method of any one of claims 1-54 wherein the antibody or antibody fragment is administered intravenously.

57). The method of claim 1 or 2, wherein the CGRP-associated diarrhea is selected from diarrhea associated with irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, cholera, pancreatic disease, lactose intolerance, fructose malabsorption, malabsorption, magnesium overdose or overingestion, vitamin C overdose or overingestion, sorbitol overdose or overingestion, food poisoning, *E. coli* infection, enzyme deficiency, mucosal abnormality, celiac disease, gluten intolerance, pernicious anemia, food allergy, food intolerance, short bowel syndrome, radiation fibrosis, diarrhea

associated with chemotherapy, orlistat treatment, cystic fibrosis, pancreatitis, chronic ethanol ingestion, ischemic bowel disease, microscopic colitis, bile salt malabsorption (primary bile acid diarrhea), elevated seratonin secretion or levels, or toddler's diarrhea.

58). The method of claim 1 or 2, wherein the treatment further includes the administration of another therapeutic agent or regimen selected from the group consisting of: antibiotics, antivirals, absorbents, anti-motility medications, bismuth compounds, bismuth subsalicylate, bile acid sequestrants, probiotics, digestive enzymes, lactase, zinc, oral rehydration therapy, and any combination thereof.

59). The method of claim 58, wherein said anti-motility agents are selected from the group consisting of loperamide (Imodium), diphenoxylate with atropine (Lomotil), opiates, paregoric tincture of opium, codeine, and morphine.

60) The method of claim 58, wherein said bile acid sequestrants are selected from the group consisting of: cholestyramine, colestipol and colesevelam.

61). The method of claim 1 or 2, wherein the anti-CGRP antibody or antibody fragment having binding specificity for CGRP comprises variable light chain CDR1, CDR2, and CDR3 polypeptide sequences and variable heavy chain CDR1, CDR2, and CDR3 polypeptide sequences selected from the following:

	V_L CDR1	V_L CDR2	V_L CDR3	V_H CDR1	V_H CDR2	V_H CDR3
A	Seq ID No: 5	Seq ID No: 6	Seq ID No: 7	Seq ID No: 8	Seq ID No: 9	Seq ID No: 10
B	Seq ID No: 15	Seq ID No: 16	Seq ID No: 17	Seq ID No: 18	Seq ID No: 19	Seq ID No: 20
C	Seq ID No: 25	Seq ID No: 26	Seq ID No: 27	Seq ID No: 28	Seq ID No: 29	Seq ID No: 30
D	Seq ID No: 35	Seq ID No: 36	Seq ID No: 37	Seq ID No: 38	Seq ID No: 39	Seq ID No: 40
E	Seq ID No: 45	Seq ID No: 46	Seq ID No: 47	Seq ID No: 48	Seq ID No: 49	Seq ID No: 50
F	Seq ID No: 55	Seq ID No: 56	Seq ID No: 57	Seq ID No: 58	Seq ID No: 59	Seq ID No: 60
G	Seq ID	Seq ID	Seq ID	Seq ID	Seq ID	Seq ID

	No: 65	No: 66	No: 67	No: 68	No: 69	No: 70
H	Seq ID No: 75	Seq ID No: 76	Seq ID No: 77	Seq ID No: 78	Seq ID No: 79	Seq ID No: 80
I	Seq ID No: 85	Seq ID No: 86	Seq ID No: 87	Seq ID No: 88	Seq ID No: 89	Seq ID No: 90
J	Seq ID No: 95	Seq ID No: 96	Seq ID No: 97	Seq ID No: 98	Seq ID No: 99	Seq ID No: 100
K	Seq ID No: 105	Seq ID No: 106	Seq ID No: 107	Seq ID No: 108	Seq ID No: 109	Seq ID No: 110
L	Seq ID No: 115	Seq ID No: 116	Seq ID No: 117	Seq ID No: 118	Seq ID No: 119	Seq ID No: 120
M	Seq ID No: 125	Seq ID No: 126	Seq ID No: 127	Seq ID No: 128	Seq ID No: 129	Seq ID No: 130
N	Seq ID No: 135	Seq ID No: 136	Seq ID No:137	Seq ID No: 138	Seq ID No: 139	Seq ID No: 140

62). The method of claim 61, wherein said antibody or antibody fragment is an scFv, camelbody, nanobody, IgNAR (single-chain antibodies derived from sharks), Fab, Fab', or F(ab')2 fragment.

63). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment is a Fab fragment.

64). The method of claim 61, wherein said antibody or antibody fragment comprises a variable light chain polypeptide sequence and a variable heavy chain polypeptide sequence selected from the following:

	Variable Light Chain	Variable Heavy Chain
A	Seq ID No: 1	Seq ID No: 3
B	Seq ID No: 11	Seq ID No: 13
C	Seq ID No: 21	Seq ID No: 23
D	Seq ID No: 31	Seq ID No: 33
E	Seq ID No: 41	Seq ID No: 43
F	Seq ID No: 51	Seq ID No: 53
G	Seq ID No: 61	Seq ID No: 63
H	Seq ID No: 71	Seq ID No: 73
I	Seq ID No: 81	Seq ID No: 83
J	Seq ID No: 91	Seq ID No: 93

K	Seq ID No: 101	Seq ID No: 103
L	Seq ID No: 111	Seq ID No: 113
M	Seq ID No: 121	Seq ID No: 123
N	Seq ID No: 131	Seq ID No: 133

65). The method of claim 61, wherein said antibody or antibody fragment comprises a light chain polypeptide sequence and a heavy chain polypeptide sequence selected from the following:

	Light Chain	Heavy Chain
Ab1	Seq ID No: 2	Seq ID No: 4
Ab2	Seq ID No: 12	Seq ID No: 14
Ab3	Seq ID No: 22	Seq ID No: 24
Ab4	Seq ID No: 32	Seq ID No: 34
Ab5	Seq ID No: 42	Seq ID No: 44
Ab6	Seq ID No: 52	Seq ID No: 54
Ab7	Seq ID No: 62	Seq ID No: 64
Ab8	Seq ID No: 72	Seq ID No: 74
Ab9	Seq ID No: 82	Seq ID No: 84
Ab10	Seq ID No: 92	Seq ID No: 94
Ab11	Seq ID No: 102	Seq ID No: 104
Ab12	Seq ID No: 112	Seq ID No: 114
Ab13	Seq ID No: 122	Seq ID No: 124
Ab14	Seq ID No: 132	Seq ID No: 134

66). The method of claim 61, wherein said antibody or antibody fragment comprises a variable light chain and variable heavy chain polypeptide sequences are each at least 90% identical to one of the variable light chain polypeptide sequences of SEQ ID NOS: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, or 131, and one of the variable heavy chain polypeptide sequences of SEQ ID NOS: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123 or 133, respectively.

67). The method of claim 61, wherein said antibody or antibody fragment is chimeric or humanized.

68). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment is entirely aglycosylated or lacks N-glycosylation or comprises only mannose residues.

69). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment comprises a human constant domain.

70). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment is an IgG1, IgG2, IgG3 or IgG4 antibody.

71). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment contains an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, and/or glycosylation.

72). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment has an Fc region that contains a mutation that alters or eliminates glycosylation or eliminates N-glycosylation.

73). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment is directly or indirectly attached to a detectable label or therapeutic agent.

74). The method of claim 61, wherein said anti-CGRP antibody or antibody fragment further comprises an effector moiety.

75). The method of claim 74, wherein said effector moiety is a detectable moiety or a functional moiety.

76). The method of claim 75, wherein said detectable moiety is a fluorescent dye, an enzyme, a substrate, a bioluminescent material, a radioactive material, or a chemiluminescent material.

77). The method of claim 75, wherein said functional moiety is streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, or a radioactive material.

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Ab1

Ab1 Heavy chain (chimera) Full length protein sequence.

QSLEESGGRLVTPGTPLTLTCTVSGLDLSSYYMQWVRQAPGKGLEWIGVIGINDNTYYASWAKGRFTISRASSTTVDLKMTS
LTTEDTATYFCARGDIWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 4)

Ab1 Variable region heavy chain (chimera) protein sequence.

QSLEESGGRLVTPGTPLTLTCTVSGLDLSSYYMQWVRQAPGKGLEWIGVIGINDNTYYASWAKGRFTISRASSTTVDLKMTS
LTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 3)

Ab1 Variable region heavy chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QSLEESGGRLVTPGTPLTLTCTVSGLDLS**SYYMQ**WVRQAPGKGLEWIGVIGINDNTYYASWAKGRFTISRASSTTVDLKMTS
LTTEDTATYFCAR*GDI*WGPGTLVTVSS (SEQ ID NOS: 8, 9, 10, respectively)

Ab1 Variable region heavy chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGACTCG
ACCTCAGT**AGCTACTACATGCAA**ATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTATTA
ATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGCCTCGTCGACCACGGTGGATCTGA
AAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA*GGGGACATC*TGGGGCCCAGGCACCCTCGT
CACCGTCTCGAGC (SEQ ID NO: 143)

FIG. 1

Ab1 Heavy chain (chimera) Full length DNA sequence.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGACTCG
ACCTCAGTAGCTACTACATGCAATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTATTA
ATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGCCTCGTCGACCACGGTGGATCTGA
AAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAG
CGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC
AGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC
AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCC
CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAG
ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAG
TACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG
GTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATC
CCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 144)

Ab1 Light chain (chimera) Full length protein sequence.

QVLTQTASPVSAAVGSTVTINCQASQSVYDNNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDLECAD
AATYYCLGSYDCSSGDCFVFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 2)

Ab1 Variable region light chain (chimera) protein sequence.

QVLTQTASPVSAAVGSTVTINCQASQSVYDNNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDLECAD
AATYYCLGSYDCSSGDCFVFGGGTEVVVKR (SEQ ID NO: 1)

FIG. 1 (Continued)

Ab1 Variable region light chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQTASPVSAAVGSTVTINC**QASQSVYDNNYLA**WYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDLECA
DAATYYC*LGSYDCSSGDCFV*FGGGTEVVVKR (SEQ ID NOS: 5, 6, 7, respectively)

Ab1 Variable region light chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGC**CAGGCCAGTCAG**
AGTGTTTATGATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTAC
ATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGAC
CTGGAGTGTGCCGATGCTGCCACTTACTACTGT*CTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTT*TTCGGCGGAG
GGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 141)

Ab1 Light chain (chimera) Full length DNA sequence.

CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGCCAGGCCAGTCAG
AGTGTTTATGATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTACAT
CCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACCT
GGAGTGTGCCGATGCTGCCACTTACTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGGAG
GGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC
CTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG
ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC
ACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 142)

FIG. 1 (Continued)

Ab2

Ab2 Heavy chain (humanized) Full length protein sequence – mammalian produced.

EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGINDNTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 14)

Ab2 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGINDNTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 13)

Ab2 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGLDLS**SYYMQ**WVRQAPGKGLEWVGVIGINDNTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCAR*GDI*WGQGTLVTVSS (SEQ ID NOS: 18, 19, 20, respectively)

Ab2 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAC
TCGACCTCAGT**AGCTACTACATGCAA**TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
TCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA*GGGGACATC*TGGGGCCAAGGGAC
CCTCGTCACCGTCTCGAGC (SEQ ID NO: 153)

FIG. 2

Ab2 Heavy chain (humanized) Full length DNA sequence – mammalian produced.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAC
TCGACCTCAGTAGCTACTACATGCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
TCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 154)

Ab2 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSSGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 12)

Ab2 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSSGDCFVFGGGTKVEIKR (SEQ ID NO: 11)

FIG. 2 (Continued)

Ab2 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**QASQSVYDNNYLA**WYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCSSGDCFV*FGGGTKVEIKR (SEQ ID NOS: 15, 16, 17, respectively)

Ab2 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CAGGCCAGTCAG**
AGTGTTTATGATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTAC
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTT*TTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 151)

Ab2 Light chain (humanized) Full length DNA sequence.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCAGTCAGA
GTGTTTATGATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTACATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGGAGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 152)

FIG. 2 (Continued)

Ab3

Ab3 Heavy chain (humanized) Full length protein sequence – yeast produced.

EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGINDNTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 24)

Ab3 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGLDLSSYYMQWVRQAPGKGLEWVGVIGINDNTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 23)

Ab3 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGLDLS**SYYMQ**WVRQAPGKGLEWVGVIGINDNTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCAR*GDI*WGQGTLVTVSS (SEQ ID NOS: 28, 29, 30, respectively)

Ab3 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAC
TCGACCTCAGT**AGCTACTACATGCAA**TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
TCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA*GGGGACATC*TGGGGCCAAGGGAC
CCTCGTCACCGTCTCGAGC (SEQ ID NO: 163)

FIG. 3

Ab3 Heavy chain (humanized) Full length DNA sequence – yeast produced.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAC
TCGACCTCAGTAGCTACTACATGCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
TCAATGATAACACACATACTACGCCGAGCTGGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGGCTGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGGCCTCCACCAAGGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 164)

Ab3 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSSGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 22)

Ab3 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYDNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSSGDCFVFGGGTKVEIKR (SEQ ID NO: 21)

FIG. 3 (Continued)

Ab3 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**QASQSVYDNNYLA**WYQQKPGKVPKQLIY**STSTLAS**GVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCSSGDCFV*FGGGTKVEIKR (SEQ ID NOS: 25, 26, 27, respectively)

Ab3 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CAGGCCAGTCAG**
AGTGTTTATGATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTAC
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTCGGCGGAG*
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 161)

Ab3 Light chain (humanized) Full length DNA sequence.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCAGTCAGA
GTGTTTATGATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTACATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTCGGCGGAGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 162)

FIG. 3 (Continued)

Ab4

Ab4 Heavy chain (chimera) Full length protein sequence.

QSLEESGGRLVTPGTPLTLTCSVSGIDLSGYYMNWVRQAPGKGLEWIGVIGINGATYYASWAKGRFTISKTSSTTVDLKMTS
LTTEDTATYFCARGDIWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 34)

Ab4 Variable region heavy chain (chimera) protein sequence.

QSLEESGGRLVTPGTPLTLTCSVSGIDLSGYYMNWVRQAPGKGLEWIGVIGINGATYYASWAKGRFTISKTSSTTVDLKMTS
LTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 33)

Ab4 Variable region heavy chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QSLEESGGRLVTPGTPLTLTCSVSGIDLS**GYYMN**WVRQAPGKGLEWIGVIGINGATYYASWAKGRFTISKTSSTTVDLKMTS
LTTEDTATYFCAR*GDI*WGPGTLVTVSS (SEQ ID NOS: 38, 39, 40, respectively)

Ab4 Variable region heavy chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGTTCCGTCTCTGGCATCG
ACCTCAGT**GGCTACTACATGAAC**TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTATT
AATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTG
AAAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA*GGGGACATC*TGGGGCCCGGGCACCCTC
GTCACCGTCTCGAGC (SEQ ID NO: 173)

FIG. 4

Ab4 Heavy chain (chimera) Full length DNA sequence.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGTTCCGTCTCTGGCATCG
ACCTCAGTGGCTACTACATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTATTA
ATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGA
AAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCGGGCACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAG
CGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC
AGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC
AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCC
CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAG
ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAG
TACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG
GTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATC
CCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 174)

Ab4 Light chain (chimera) Full length protein sequence.

QVLTQTPSPVSAAVGSTVTINCQASQSVYHNTYLAWYQQKPGQPPKQLIYDASTLASGVPSRFSGSGSGTQFTLTISGVQCND
AAAYYCLGSYDCTNGDCFVFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 32)

Ab4 Variable region light chain (chimera) protein sequence.

QVLTQTPSPVSAAVGSTVTINCQASQSVYHNTYLAWYQQKPGQPPKQLIYDASTLASGVPSRFSGSGSGTQFTLTISGVQCND
AAAYYCLGSYDCTNGDCFVFGGGTEVVVKR (SEQ ID NO: 31)

FIG. 4 (Continued)

Ab4 Variable region light chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQTPSPVSAAVGSTVTINC**QASQSVYHNTYLA**WYQQKPGQPPKQLIY<u>DASTLAS</u>GVPSRFSGSGSGTQFTLTISGVQCN
DAAAYYC*LGSYDCTNGDCFV*FGGGTEVVVKR (SEQ ID NOS: 35, 36, 37, respectively)

Ab4 Variable region light chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGC**CAGGCCAGTCAG**
AGTGTTTATCATAACACCTACCTGGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAACAACTGATCTATG<u>ATGC</u>
<u>ATCCACTCTGGCGTCT</u>GGGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGGC
GTGCAGTGTAACGATGCTGCCGCTTACTACTGT*CTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAG*
GGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 171)

Ab4 Light chain (chimera) Full length DNA sequence.

CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGCCAGGCCAGTCAGA
GTGTTTATCATAACACCTACCTGGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAACAACTGATCTATGATGCATC
CACTCTGGCGTCTGGGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGGCGTG
CAGTGTAACGATGCTGCCGCTTACTACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAGG
GACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 172)

FIG. 4 (Continued)

Ab5

Ab5 Heavy chain (humanized) Full length protein sequence – mammalian produced.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 44)

Ab5 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 43)

Ab5 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLS**GYYMN**WVRQAPGKGLEWVGVIGINGATYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCAR*GDI*WGQGTLVTVSS (SEQ ID NOS: 48, 49, 50, respectively)

Ab5 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACCTCAGT**GGCTACTACATGAAC**TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGT
ATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTG
TATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA*GGGGACATC*TGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 183)

FIG. 5

Ab5 Heavy chain (humanized) Full length DNA sequence – mammalian produced.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACCTCAGTGGCTACTACATGAACTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
TTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 184)

Ab5 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCTNGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 42)

Ab5 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCTNGDCFVFGGGTKVEIKR (SEQ ID NO: 41)

FIG. 5 (Continued)

Ab5 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**QASQSVYHNTYLA**WYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCTNGDCFV*FGGGTKVEIKR (SEQ ID NOS: 45, 46, 47, respectively)

Ab5 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CAGGCCAGTCAG**
AGTGTTTATCATAACACCTACCTGGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATGC
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTT*TTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 181)

Ab5 Light chain (humanized) Full length DNA sequence.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCAGTCAGA
GTGTTTATCATAACACCTACCTGGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATGCATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 182)

FIG. 5 (Continued)

Ab6

Ab6 Heavy chain (humanized) Full length protein sequence – yeast produced.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 54)

Ab6 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYYMNWVRQAPGKGLEWVGVIGINGATYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 53)

Ab6 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLS**GYYMN**WVRQAPGKGLEWVGVIGINGATYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCAR*GDI*WGQGTLVTVSS (SEQ ID NOS: 58, 59, 60, respectively)

Ab6 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACCTCAGT**GGCTACTACATGAAC**TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGT
ATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTG
TATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA*GGGGACATC*TGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 193)

FIG. 6

Ab6 Heavy chain (humanized) Full length DNA sequence – yeast produced.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACCTCAGTGGCTACTACATGAACTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
TTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGGCTGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAGCGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 194)

Ab6 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCTNGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 52)

Ab6 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCTNGDCFVFGGGTKVEIKR (SEQ ID NO: 51)

FIG. 6 (Continued)

Ab6 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**QASQSVYHNTYLA**WYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCTNGDCFV*FGGGTKVEIKR (SEQ ID NOS: 55, 56, 57, respectively)

Ab6 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CAGGCCAGTCAG**
AGTGTTTATCATAACACCTACCTGGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATGC
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTT*TTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 191)

Ab6 Light chain (humanized) Full length DNA sequence.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCAGTCAGA
GTGTTTATCATAACACCTACCTGGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATGCATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 192)

FIG. 6 (Continued)

Ab7

Ab7 Heavy chain (chimera) Full length protein sequence.

QEQLKESGGRLVTPGTSLTLTCTVSGIDLSNHYMQWVRQAPGKGLEWIGVVGINGRTYYASWAKGRFTISRTSSTTVDLKM
TRLTTEDTATYFCARGDIWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 64)

Ab7 Variable region heavy chain (chimera) protein sequence.

QEQLKESGGRLVTPGTSLTLTCTVSGIDLSNHYMQWVRQAPGKGLEWIGVVGINGRTYYASWAKGRFTISRTSSTTVDLKM
TRLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 63)

Ab7 Variable region heavy chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QEQLKESGGRLVTPGTSLTLTCTVSGIDLS**NHYMQ**WVRQAPGKGLEWIGVVGINGRTYYASWAKGRFTISRTSSTTVDLKM
TRLTTEDTATYFCAR*GDI*WGPGTLVTVSS (SEQ ID NOS: 68, 69, 70, respectively)

Ab7 Variable region heavy chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACATCCCTGACACTCACCTGCACCGTCTCTGGA
ATCGACCTCAGT**AACCACTACATGCAA**TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCGTTGG
TATTAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAACCTCGTCGACCACGGTGGAT
CTGAAAATGACCAGGCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA*GGGGACATC*TGGGGCCCAGGCACC
CTGGTCACCGTCTCGAGC (SEQ ID NO: 203)

FIG. 7

Ab7 Heavy chain (chimera) Full length DNA sequence.

CAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACATCCCTGACACTCACCTGCACCGTCTCTGGA
ATCGACCTCAGTAACCACTACATGCAATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCGTTGGT
ATTAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAACCTCGTCGACCACGGTGGAT
CTGAAAATGACCAGGCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGGGGACATCTGGGGCCCAGGCACC
CTGGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGG
GCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGA
CCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC
CAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGA
GCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTC
TTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACG
AAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG
CAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAG
TGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCA
CAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTC
TATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTG
GACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCAT
GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID
NO: 204)

Ab7 Light chain (chimera) Full length protein sequence.

QVLTQTASPVSAAVGSTVTINCQASQSVYNYNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDVQCD
DAATYYCLGSYDCSTGDCFVFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 62)

Ab7 Variable region light chain (chimera) protein sequence.

QVLTQTASPVSAAVGSTVTINCQASQSVYNYNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDVQCD
DAATYYCLGSYDCSTGDCFVFGGGTEVVVKR (SEQ ID NO: 61)

FIG. 7 (Continued)

Ab7 Variable region light chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQTASPVSAAVGSTVTINC**QASQSVYNYNYLA**WYQQKPGQPPKQLIY<u>STSTLAS</u>GVSSRFKGSGSGTQFTLTISDVQCD
DAATYYC*LGSYDCSTGDCFV*FGGGTEVVVKR (SEQ ID NOS: 65, 66, 67, respectively)

Ab7 Variable region light chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCAATTGC**CAGGCCAGTCAG**
AGTGTTTATAATTACAACTACCTTGCCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATT<u>CTACA</u>
<u>TCCACTCTGGCATCT</u>GGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACG
TGCAGTGTGACGATGCTGCCACTTACTACTGT*CTAGGCAGTTATGACTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGAGG*
GACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 201)

Ab7 Light chain (chimera) Full length DNA sequence.

CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCAATTGCCAGGCCAGTCAG
AGTGTTTATAATTACAACTACCTTGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTACAT
CCACTCTGGCATCTGGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACGT
GCAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCAGTTATGACTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGAG
GGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC
CTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG
ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC
ACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 202)

FIG. 7 (Continued)

Ab8

Ab8 Heavy chain (humanized) Full length protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSNHYMQWVRQAPGKGLEWVGVVGINGRTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 74)

Ab8 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSNHYMQWVRQAPGKGLEWVGVVGINGRTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 73)

Ab8 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGIDLS**NHYMQ**WVRQAPGKGLEWVGVVGINGRTYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCAR*GDI*WGQGTLVTVSS (SEQ ID NOS: 78, 79, 80, respectively)

Ab8 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACCTCAGT**AACCACTACATGCAA**TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCGTTGGTA
TCAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCTAGA*GGGGACATC*TGGGGCCAAGGGAC
CCTCGTCACCGTCTCGAGC (SEQ ID NO: 213)

FIG. 8

Ab8 Heavy chain (humanized) Full length DNA sequence.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACCTCAGTAACCACTACATGCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCGTTGGTA
TCAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 214)

Ab8 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYNYNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSTGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 72)

Ab8 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQSVYNYNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSTGDCFVFGGGTKVEIKR (SEQ ID NO: 71)

FIG. 8 (Continued)

Ab8 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**QASQSVYNYNYLA**WYQQKPGKVPKQLIY**STSTLAS**GVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCSTGDCFV*FGGGTKVEIKR (SEQ ID NOS: 75, 76, 77, respectively)

Ab8 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CAGGCCAGTCAG**
AGTGTTTACAATTACAACTACCTTGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATT**CTAC**
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTGGGCAGTTATAGATTGATTATGTTTTGTTTCGGCGGAG*
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 211)

Ab8 Light chain (humanized) Full length DNA sequence.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCAGTCAGA
GTGTTTACAATTACAACTACCTTGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTACATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTGGGCAGTTATAGTACTGGTGATTATTTTGTTTTCGGCGGAGGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 212)

FIG. 8 (Continued)

Ab9

Ab9 Heavy chain (chimera) Full length protein sequence.

QSLEESGGRLVTPGTPLTLTCTVSGIGLSSYYMQWVRQSPGRGLEWIGVIGSDGKTYYATWAKGRFTISKTSSTTVDLRMAS
LTTEDTATYFCTRGDIWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 84)

Ab9 Variable region heavy chain (chimera) protein sequence.

QSLEESGGRLVTPGTPLTLTCTVSGIGLSSYYMQWVRQSPGRGLEWIGVIGSDGKTYYATWAKGRFTISKTSSTTVDLRMAS
LTTEDTATYFCTRGDIWGPGTLVTVSS (SEQ ID NO: 83)

Ab9 Variable region heavy chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QSLEESGGRLVTPGTPLTLTCTVSGIGLS**SYYMQ**WVRQSPGRGLEWIGVIGSDGKTYYATWAKGRFTISKTSSTTVDLRMAS
LTTEDTATYFCTR*GDI*WGPGTLVTVSS (SEQ ID NOS: 88, 89, 90, respectively)

Ab9 Variable region heavy chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGAATCG
GCCTCAGT**AGCTACTACATGCAG**TGGGTCCGCCAGTCTCCAGGGAGGGGGCTGGAATGGATCGGAGTCATTGGTAGT
GATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAAGACCTCGTCGACCACGGTGGATCTG
AGAATGGCCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTACCAGA*GGGGACATC*TGGGGCCCGGGGACCCTC
GTCACCGTCTCGAGC (SEQ ID NO: 223)

FIG. 9

Ab9 Heavy chain (chimera) Full length DNA sequence.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGCACAGTCTCTGGAATCG
GCCTCAGTAGCTACTACATGCAGTGGGTCCGCCAGTCTCCAGGGAGGGGGCTGGAATGGATCGGAGTCATTGGTAGTG
ATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAAGACCTCGTCGACCACGGTGGATCTGA
GAATGGCCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTACCAGAGGGGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAG
CGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC
AGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC
AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCC
CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAG
ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAG
TACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG
GTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATC
CCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 224)

Ab9 Light chain (chimera) Full length protein sequence.

QVLTQTPSPVSAAVGSTVTINCQASQNVYNNNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFRGSGSGTQFTLTISDVQCD
DAATYYCLGSYDCSRGDCFVFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 82)

Ab9 Variable region light chain (chimera) protein sequence.

QVLTQTPSPVSAAVGSTVTINCQASQNVYNNNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFRGSGSGTQFTLTISDVQCD
DAATYYCLGSYDCSRGDCFVFGGGTEVVVKR (SEQ ID NO: 81)

FIG. 9 (Continued)

Ab9 Variable region light chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQTPSPVSAAVGSTVTINC**QASQNVYNNNYLA**WYQQKPGQPPKQLIY<u>STSTLAS</u>GVSSRFRGSGSGTQFTLTISDVQCD
DAATYYC*LGSYDCSRGDCFV*FGGGTEVVVKR (SEQ ID NOS: 85, 86, 87, respectively)

Ab9 Variable region light chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGC**CAGGCCAGTCAG**
AATGTTTATAATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATT<u>CTAC</u>
<u>GTCCACTCTGGCATCTGGGGTCTCATCGCGATTCAGAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGAC</u>
GTGCAGTGTGACGATGCTGCCACTTACTACTGT*CTAGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAG*
GGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 221)

Ab9 Light chain (chimera) Full length DNA sequence.

CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAGCACAGTCACCATCAATTGCCAGGCCAGTCAGA
ATGTTTATAATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTACGTC
CACTCTGGCATCTGGGGTCTCATCGCGATTCAGAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACGTG
CAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAGG
GACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGGACAGCAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 222)

FIG. 9 (Continued)

Ab10

Ab10 Heavy chain (humanized) Full length protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSDGKTYYATWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCTRGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 94)

Ab10 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSDGKTYYATWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCTRGDIWGQGTLVTVSS (SEQ ID NO: 93)

Ab10 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGIGLS**SYYMQ**WVRQAPGKGLEWVGVIGSDGKTYYATWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCTR*GDI*WGQGTLVTVSS (SEQ ID NOS: 98, 99, 100, respectively)

Ab10 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGGCCTCAGT**AGCTACTACATGCAA**ATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
GTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTACCAGA*GGGGACATC*TGGGGCCAAGGGAC
CCTCGTCACCGTCTCGAGC (SEQ ID NO: 233)

FIG. 10

Ab10 Heavy chain (humanized) Full length DNA sequence.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGGCCTCAGTAGCTACTACATGCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
GTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTACCAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 234)

Ab10 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSRGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 92)

Ab10 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSRGDCFVFGGGTKVEIKR (SEQ ID NO: 91)

FIG. 10 (Continued)

Ab10 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**QASQNVYNNNYLA**WYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCSRGDCFV*FGGGTKVEIKR (SEQ ID NOS: 95, 96, 97, respectively)

Ab10 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CAGGCCAGTCAG**
AATGTTTACAATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTAC
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTT*TTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 231)

Ab10 Light chain (humanized) Full length DNA sequence.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCAGTCAGA
ATGTTTACAATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTACATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 232)

FIG. 10 (Continued)

Ab11

Ab11 Heavy chain (chimera) Full length protein sequence.

QSLEESGGRLVTPGGSLTLTCTVSGIDVTNYYMQWVRQAPGKGLEWIGVIGVNGKRYYASWAKGRFTISKTSSTTVDLKMT
SLTTEDTATYFCARGDIWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 104)

Ab11 Variable region heavy chain (chimera) protein sequence.

QSLEESGGRLVTPGGSLTLTCTVSGIDVTNYYMQWVRQAPGKGLEWIGVIGVNGKRYYASWAKGRFTISKTSSTTVDLKMT
SLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 103)

Ab11 Variable region heavy chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QSLEESGGRLVTPGGSLTLTCTVSGIDVT**NYYMQ**WVRQAPGKGLEWIGVIGVNGKRYYASWAKGRFTISKTSSTTVDLKMT
SLTTEDTATYFCAR*GDI*WGPGTLVTVSS (SEQ ID NOS: 108, 109, 110, respectively)

Ab11 Variable region heavy chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGAGGATCCCTGACACTCACCTGCACAGTCTCTGGAATCG
ACGTCACT**AACTACTATATGCAA**TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTGTGA
ATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGA
AAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGA*GGCGACATC*TGGGGCCCGGGGACCCTCGT
CACCGTCTCGAGC (SEQ ID NO: 243)

FIG. 11

Ab11 Heavy chain (chimera) Full length DNA sequence.

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGAGGATCCCTGACACTCACCTGCACAGTCTCTGGAATCG
ACGTCACTAACTACTATATGCAATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTGTGA
ATGGTAAGAGATACTACGCCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACCTCGTCGACCACGGTGGATCTGA
AAATGACCAGTCTGACAACCGAGGACACGGCCACCTATTTCTGTGCCAGAGGCGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAG
CGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC
AGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC
AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCC
CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAG
ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAG
TACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG
GTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATC
CCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 244)

Ab11 Light chain (chimera) Full length protein sequence.

QVLTQTASPVSPAVGSTVTINCRASQSVYYNNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDVQCDD
AATYYCLGSYDCSNGDCFVFGGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 102)

Ab11 Variable region light chain (chimera) protein sequence.

QVLTQTASPVSPAVGSTVTINCRASQSVYYNNYLAWYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDVQCDD
AATYYCLGSYDCSNGDCFVFGGGTEVVVKR (SEQ ID NO: 101)

FIG. 11 (Continued)

Ab11 Variable region light chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQTASPVSPAVGSTVTINC**RASQSVYYNNYLA**WYQQKPGQPPKQLIYSTSTLASGVSSRFKGSGSGTQFTLTISDVQCD
DAATYYC*LGSYDCSNGDCFV*FGGGTEVVVKR (SEQ ID NOS: 105, 106, 107, respectively)

Ab11 Variable region light chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAGGTGCTGACCCAGACTGCATCCCCCGTGTCTCCAGCTGTGGGAAGCACAGTCACCATCAATTGC**CGGGCCAGTCAG**
AGTGTTTATTATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTAC
ATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGAC
GTGCAGTGTGACGATGCTGCCACTTACTACTGT*CTAGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTT*TTCGGCGGAG
GGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 241)

Ab11 Light chain (chimera) Full length DNA sequence.

CAGGTGCTGACCCAGACTGCATCCCCCGTGTCTCCAGCTGTGGGAAGCACAGTCACCATCAATTGCCGGGCCAGTCAGA
GTGTTTATTATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTACATC
CACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGGACACAGTTCACTCTCACCATCAGCGACGTG
CAGTGTGACGATGCTGCCACTTACTACTGTCTAGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGAGG
GACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 242)

FIG. 11 (Continued)

Ab12

Ab12 Heavy chain (humanized) Full length protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIDVTNYYMQWVRQAPGKGLEWVGVIGVNGKRYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 114)

Ab12 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIDVTNYYMQWVRQAPGKGLEWVGVIGVNGKRYYASWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCARGDIWGQGTLVTVSS (SEQ ID NO: 113)

Ab12 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGIDVT**NYYMQ**WVRQAPGKGLEWVGVIGVNGKRYYASWAKGRFTISRDNSKTTVY
LQMNSLRAEDTAVYFCAR*GDI*WGQGTLVTVSS (SEQ ID NOS: 118, 119, 120, respectively)

Ab12 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACGTCACT**AACTACTACATGCAA**TGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTG
TGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCCAGA*GGGGACATC*TGGGGCCAAGGGAC
CCTCGTCACCGTCTCGAGC (SEQ ID NO: 253)

FIG. 12

Ab12 Heavy chain (humanized) Full length DNA sequence.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGACGTCACTAACTACTACATGCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTG
TGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTGCCAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 254)

Ab12 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCRASQSVYYNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPEDV
ATYYCLGSYDCSNGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 112)

Ab12 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCRASQSVYYNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPEDV
ATYYCLGSYDCSNGDCFVFGGGTKVEIKR (SEQ ID NO: 111)

FIG. 12 (Continued)

Ab12 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**RASQSVYYNNYLA**WYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCSNGDCFV*FGGGTKVEIKR (SEQ ID NOS: 115, 116, 117, respectively)

Ab12 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CGGGCCAGTCAG**
AGTGTTTACTATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTAC
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTGGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTT*TTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 251)

Ab12 Light chain (humanized) Full length DNA sequence.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCGGGCCAGTCAGA
GTGTTTACTATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTACATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTGGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGAGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 252)

FIG. 12 (Continued)

Ab13

Ab13 Heavy chain (chimera) Full length protein sequence.

QSVEESGGGLVQPEGSLTLTCTASGFDFSSNAMWWVRQAPGKGLEWIGCIYNGDGSTYYASWVNGRFSISKTSSTTVTLQL
NSLTVADTATYYCARDLDLWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 124)

Ab13 Variable region heavy chain (chimera) protein sequence.

QSVEESGGGLVQPEGSLTLTCTASGFDFSSNAMWWVRQAPGKGLEWIGCIYNGDGSTYYASWVNGRFSISKTSSTTVTLQL
NSLTVADTATYYCARDLDLWGPGTLVTVSS (SEQ ID NO: 123)

Ab13 Variable region heavy chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QSVEESGGGLVQPEGSLTLTCTASGFDFS**SNAMW**WVRQAPGKGLEWIGCIYNGDGSTYYASWVNGRFSISKTSSTTVTLQL
NSLTVADTATYYCAR*DLDL*WGPGTLVTVSS (SEQ ID NOS: 128, 129, 130, respectively)

Ab13 Variable region heavy chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAGTCGGTGGAGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGACACTCACCTGCACAGCCTCTGGATTC
GACTTCAGT**AGCAATGCAATGTGG**TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATGCATTTACAA
TGGTGATGGCAGCACATACTACGCGAGCTGGGTGAATGGCCGATTCTCCATCTCCAAAACCTCGTCGACCACGGTGACT
CTGCAACTGAATAGTCTGACAGTCGCGGACACGGCCACGTATTATTGTGCGAGA*GATCTTGACTTG*TGGGGCCCGGGCA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 263)

FIG. 13

Ab13 Heavy chain (chimera) Full length DNA sequence.

CAGTCGGTGGAGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGACACTCACCTGCACAGCCTCTGGATTC
GACTTCAGTAGCAATGCAATGTGGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATGCATTTACAAT
GGTGATGGCAGCACATACTACGCGAGCTGGGTGAATGGCCGATTCTCCATCTCCAAAACCTCGTCGACCACGGTGACTC
TGCAACTGAATAGTCTGACAGTCGCGGACACGGCCACGTATTATTGTGCGAGAGATCTTGACTTGTGGGGCCCGGGCAC
CCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGG
GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT
CCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTG
AGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCT
CTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC
GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGA
GCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAA
GTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACC
ACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTT
CTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCT
GGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA
TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 264)

Ab13 Light chain (chimera) Full length protein sequence.

AIVMTQTPSSKSVPVGDTVTINCQASESLYNNNALAWFQQKPGQPPKRLIYDASKLASGVPSRFSGGGSGTQFTLTISGVQCD
DAATYYCGGYRSDSVDGVAFAGGTEVVVKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 122)

Ab13 Variable region light chain (chimera) protein sequence.

AIVMTQTPSSKSVPVGDTVTINCQASESLYNNNALAWFQQKPGQPPKRLIYDASKLASGVPSRFSGGGSGTQFTLTISGVQCD
DAATYYCGGYRSDSVDGVAFAGGTEVVVKR (SEQ ID NO: 121)

FIG. 13 (Continued)

Ab13 Variable region light chain (chimera) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

AIVMTQTPSSKSVPVGDTVTINC**QASESLYNNNALA**WFQQKPGQPPKRLIYDASKLASGVPSRFSGGGSGTQFTLTISGVQCD
DAATYYC*GGYRSDSVDGVA*FAGGTEVVVKR (SEQ ID NOS: 125, 126, 127, respectively)

Ab13 Variable region light chain (chimera) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GCCATCGTGATGACCCAGACTCCATCTTCCAAGTCTGTCCCTGTGGGAGACACAGTCACCATCAATTGC**CAGGCCAGT**
GAGAGTCTTTATAATAACAACGCCTTGGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATGA
TGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAGTGGCGGTGGGTCTGGGACACAGTTCACTCTCACCATCAGT
GGCGTGCAGTGTGACGATGCTGCCACTTACTACTGT*GGAGGCTACAGAAGTGATAGTGTTGATGGTGTTGCT*TTCGCCGGA
GGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 261)

Ab13 Light chain (chimera) Full length DNA sequence.

GCCATCGTGATGACCCAGACTCCATCTTCCAAGTCTGTCCCTGTGGGAGACACAGTCACCATCAATTGCCAGGCCAGTG
AGAGTCTTTATAATAACAACGCCTTGGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATGATGC
ATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAGTGGCGGTGGGTCTGGGACACAGTTCACTCTCACCATCAGTGGC
GTGCAGTGTGACGATGCTGCCACTTACTACTGTGGAGGCTACAGAAGTGATAGTGTTGATGGTGTTGCTTTCGCCGGAG
GGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC
TGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC
CTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG
ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC
ACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 262)

FIG. 13 (Continued)

Ab14

Ab14 Heavy chain (humanized) Full length protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSDGKTYYATWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCTRGDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 134)

Ab14 Variable region heavy chain (humanized) protein sequence.

EVQLVESGGGLVQPGGSLRLSCAVSGIGLSSYYMQWVRQAPGKGLEWVGVIGSDGKTYYATWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCTRGDIWGQGTLVTVSS (SEQ ID NO: 133)

Ab14 Variable region heavy chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

EVQLVESGGGLVQPGGSLRLSCAVSGIGLS**SYYMQ**WVRQAPGKGLEWVGVIGSDGKTYYATWAKGRFTISRDNSKTTVYL
QMNSLRAEDTAVYFCTR*GDI*WGQGTLVTVSS (SEQ ID NOS: 138, 139, 140, respectively)

Ab14 Variable region heavy chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGGCCTCAGT**AGCTACTACATGCAA**ATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
GTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTACCAGA*GGGGACATC*TGGGGCCAAGGGAC
CCTCGTCACCGTCTCGAGC (SEQ ID NO: 273)

FIG. 14

Ab14 Heavy chain (humanized) Full length DNA sequence.

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGAA
TCGGCCTCAGTAGCTACTACATGCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTA
GTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGACCACGGTGT
ATCTTCAAATGAACAGCCTGAGAGCTGAGGACACTGCTGTGTATTTCTGTACCAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTT
GAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA
CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG
AGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC
TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 274)

Ab14 Light chain (humanized) Full length protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSRGDCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 132)

Ab14 Variable region Light chain (humanized) protein sequence.

QVLTQSPSSLSASVGDRVTINCQASQNVYNNNYLAWYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYCLGSYDCSRGDCFVFGGGTKVEIKR (SEQ ID NO: 131)

FIG. 14 (Continued)

Ab14 Variable region Light chain (humanized) protein sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

QVLTQSPSSLSASVGDRVTINC**QASQNVYNNNYLA**WYQQKPGKVPKQLIYSTSTLASGVPSRFSGSGSGTDFTLTISSLQPED
VATYYC*LGSYDCSRGDCFV*FGGGTKVEIKR (SEQ ID NOS: 135, 136, 137, respectively)

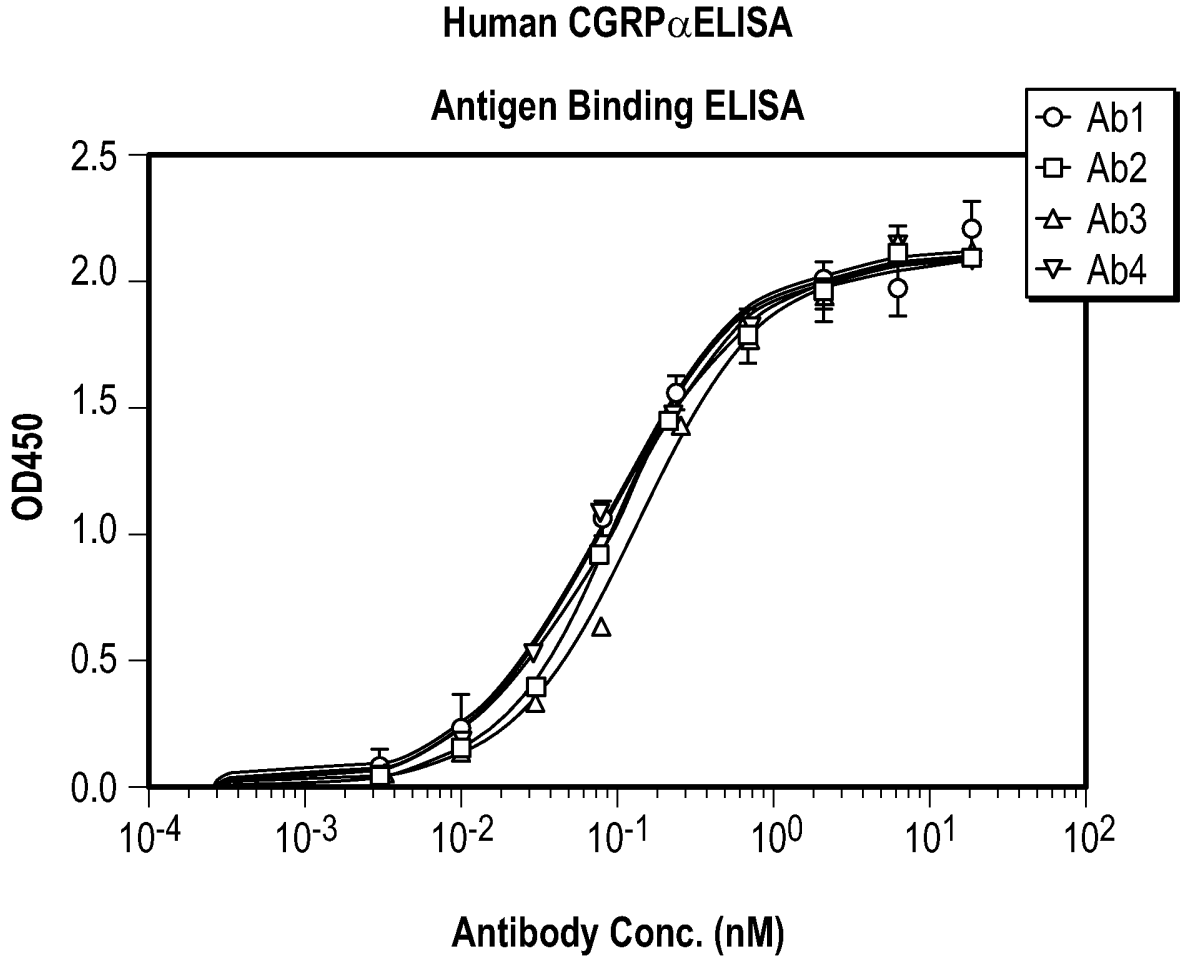
Ab14 Variable region Light chain (humanized) DNA sequence. CDR1: Bold; CDR2: Underlined; CDR3: Italics.

CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGC**CAGGCCAGTCAG**
AATGTTTACAATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTAC
ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGC
CTGCAGCCTGAAGATGTTGCAACTTATTACTGT*CTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTT*TTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 271)

Ab14 Light chain (humanized) Full length DNA sequence.

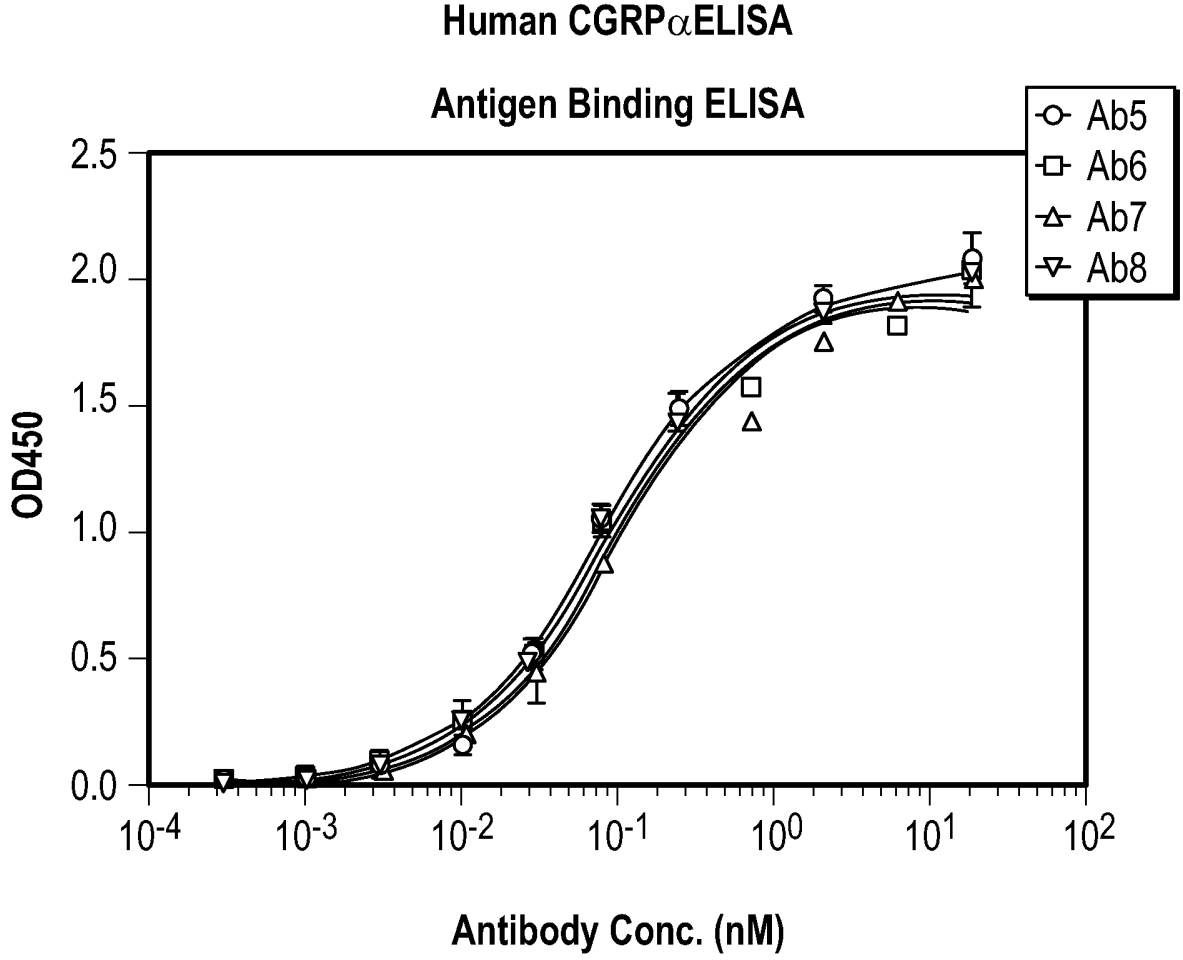
CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCCAGGCCAGTCAGA
ATGTTTACAATAACAACTACCTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTACATC
CACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGCCTGAAGATGTTGCAACTTATTACTGTCTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAGG
AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCC
TCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGA
CGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 272)

FIG. 14 (Continued)



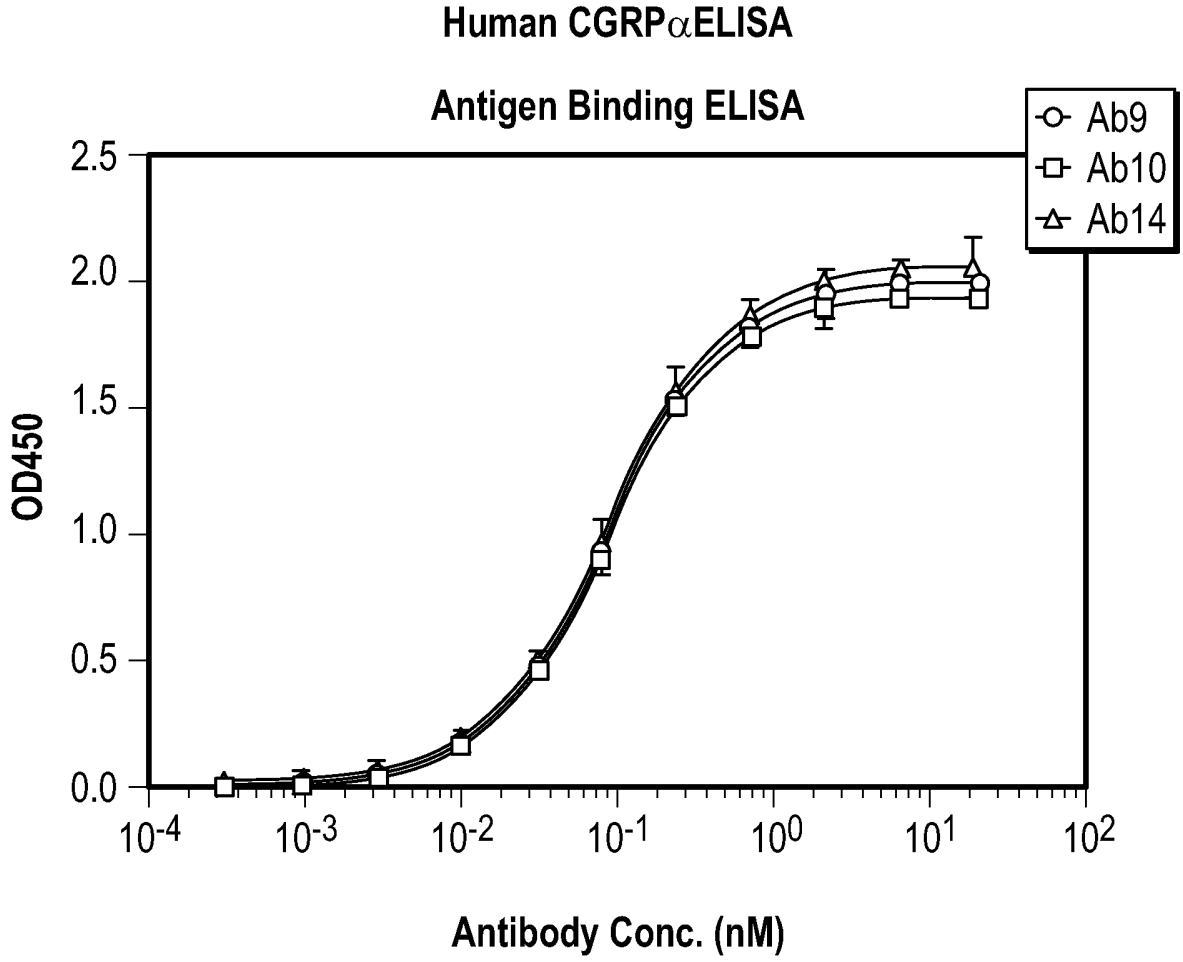
	EC50 (pM)
Ab1	103
Ab2	83
Ab3	154
Ab4	88

FIG. 15



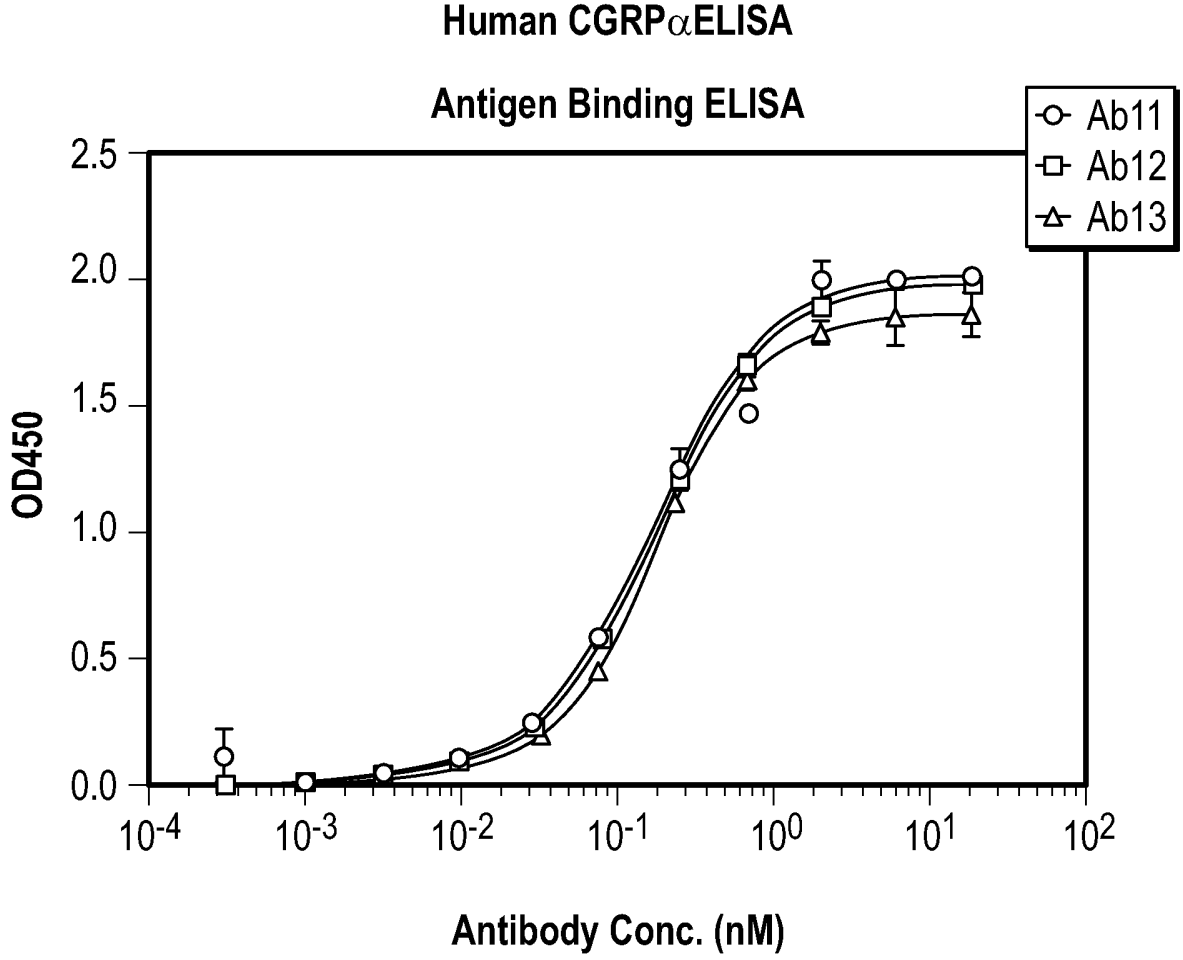
	EC50 (pM)
Ab5	103
Ab6	95
Ab7	70
Ab8	74

FIG. 16



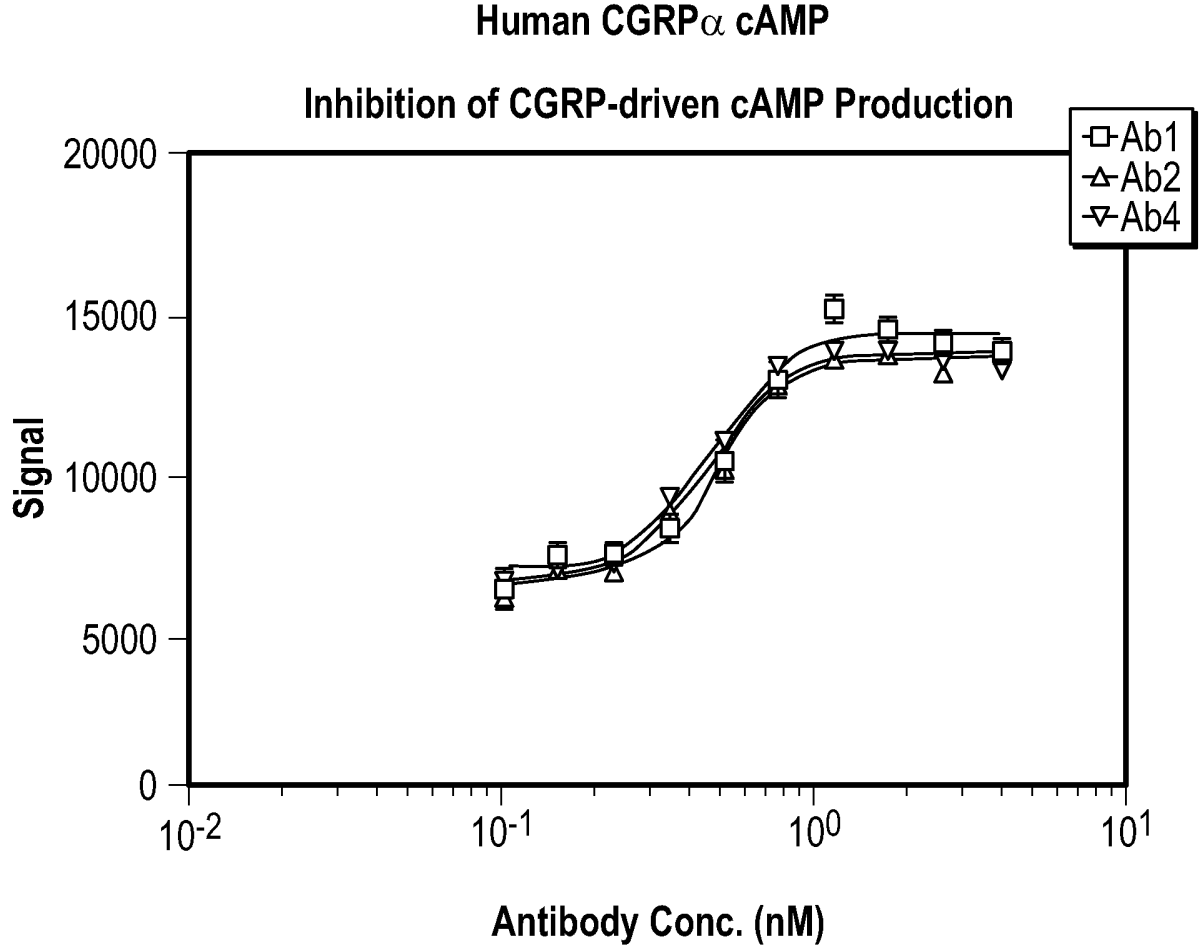
	EC50 (pM)
Ab9	79
Ab10	92
Ab14	89

FIG. 17



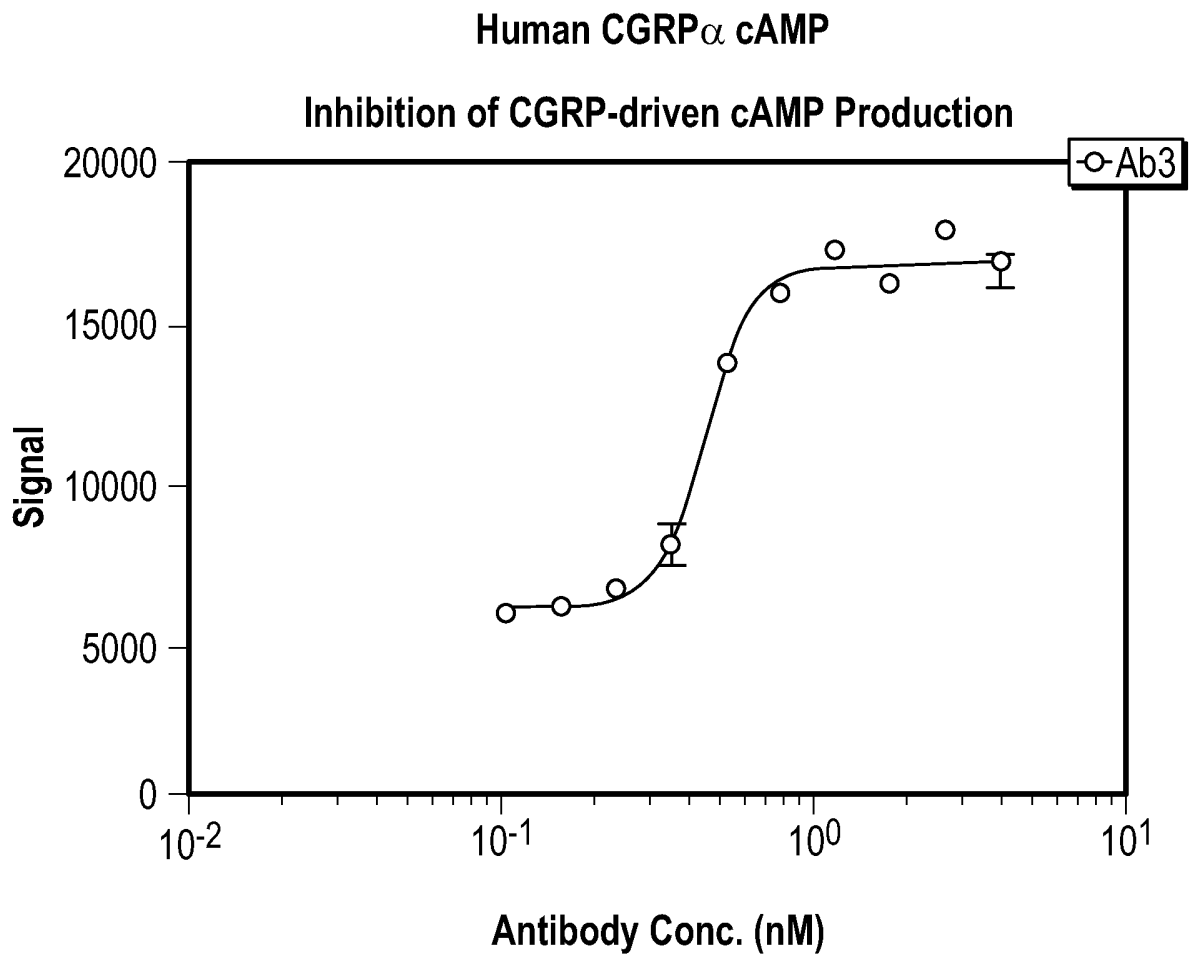
	EC50 (pM)
Ab11	184
Ab12	171
Ab13	188

FIG. 18



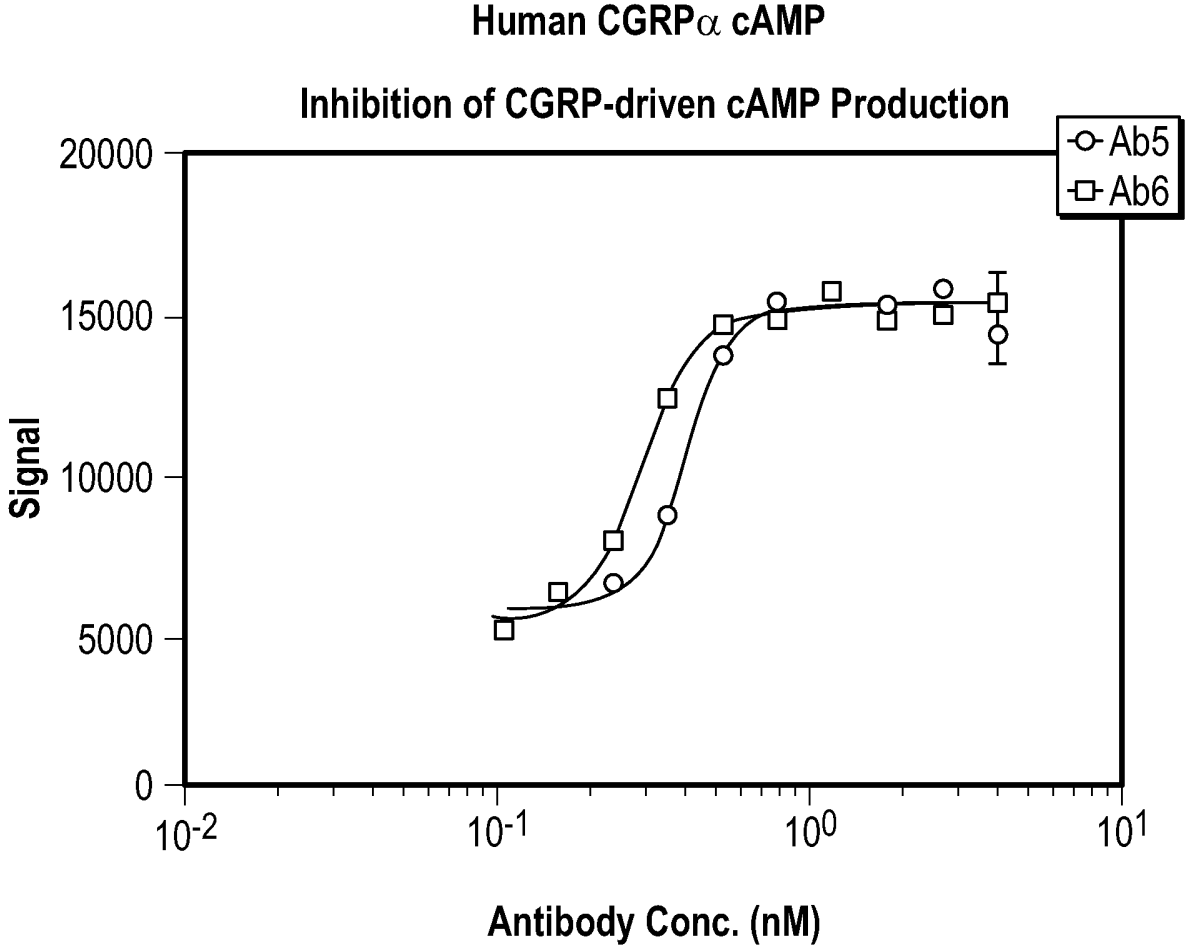
	IC50 (pM)
Ab1	531
Ab2	452
Ab4	429

FIG. 19



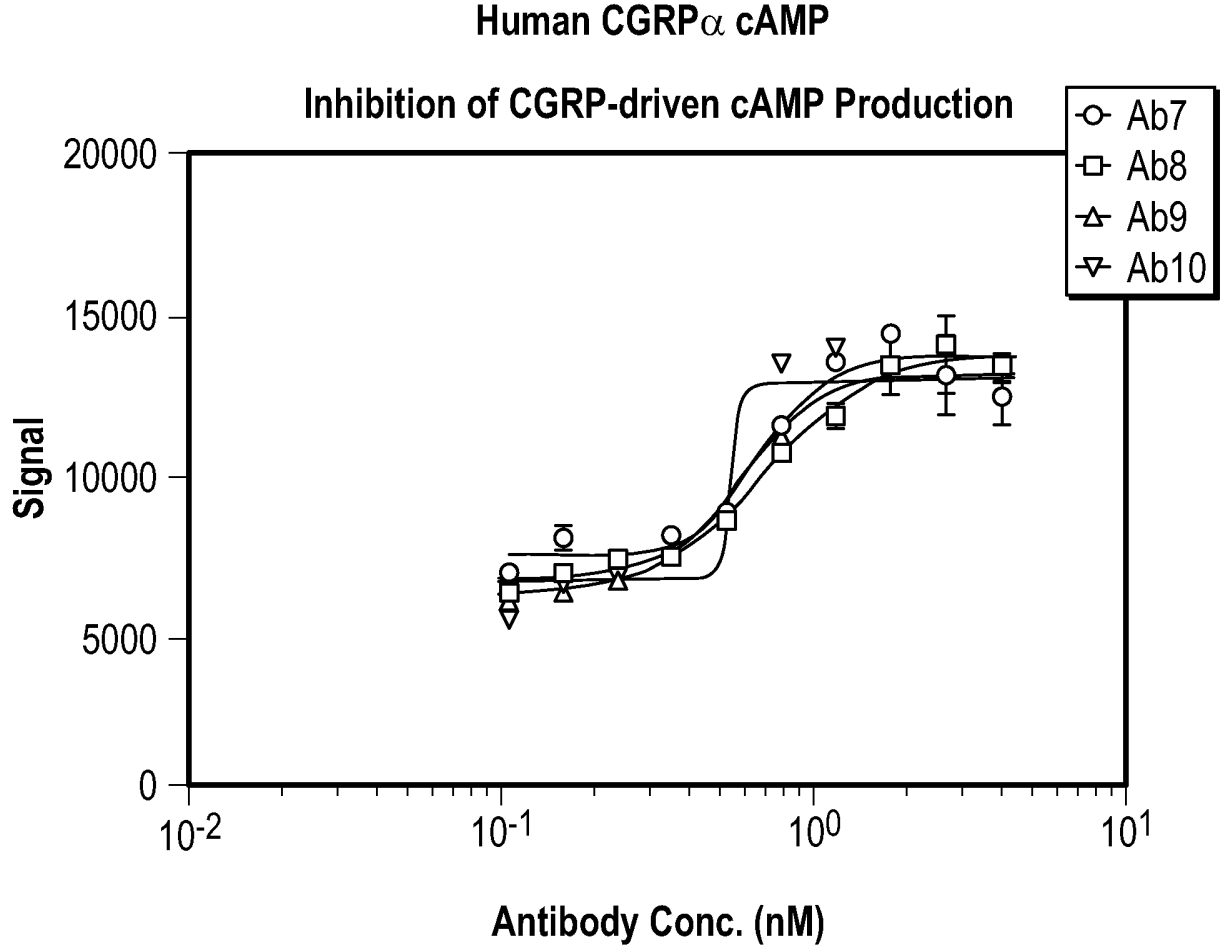
	IC50 (pM)
Ab3	452

FIG. 20



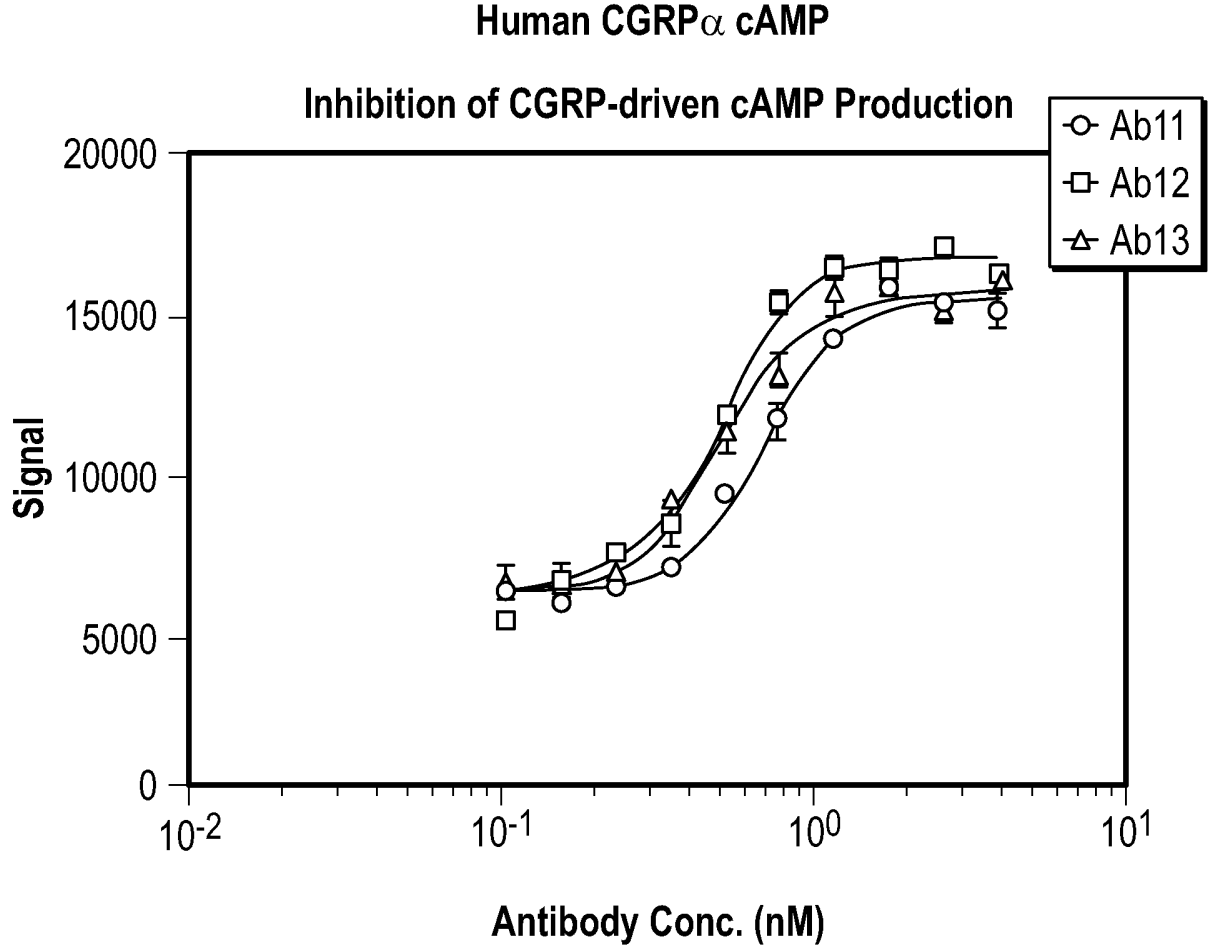
	IC50 (pM)
Ab5	400
Ab6	288

FIG. 21



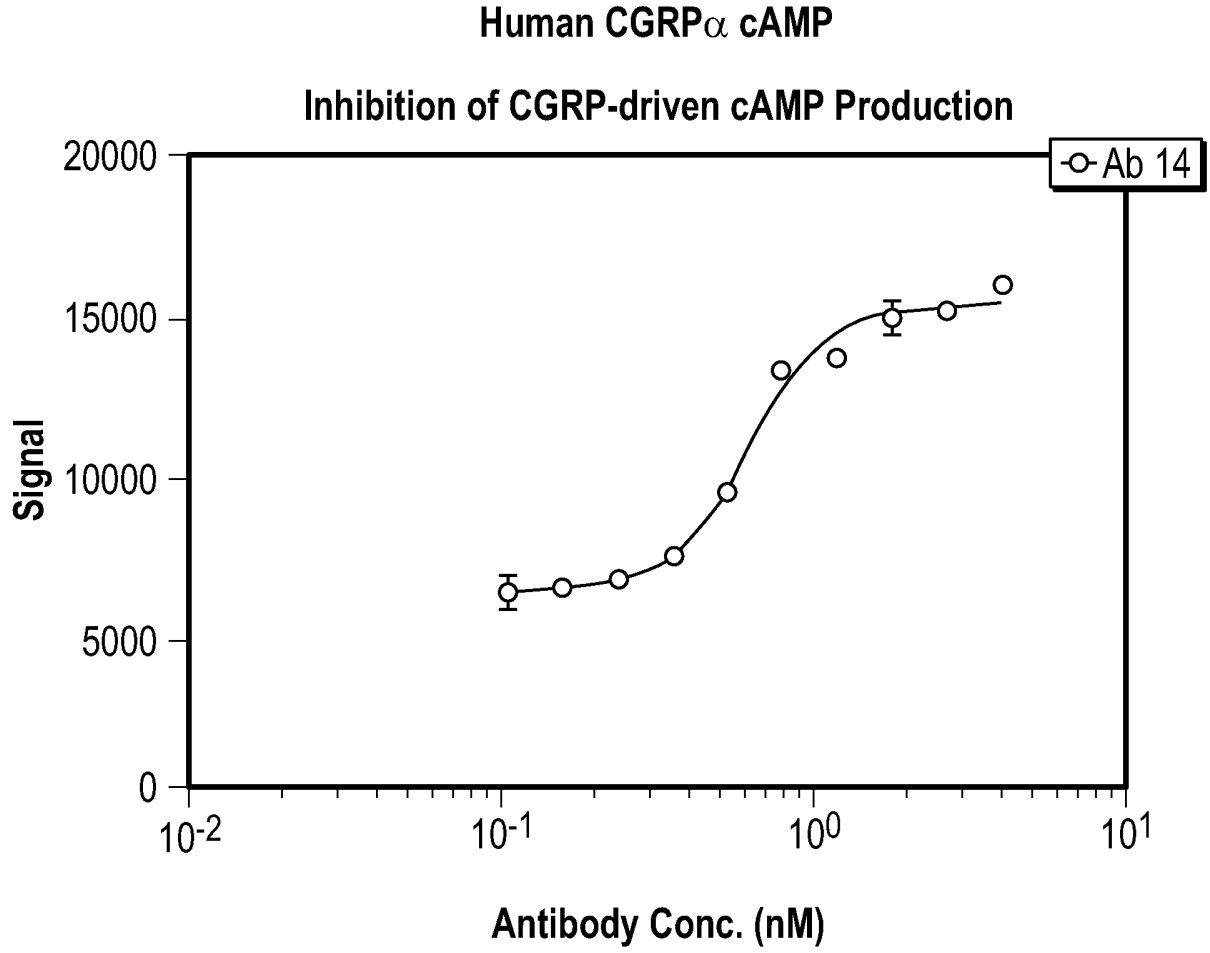
	IC50 (pM)
Ab7	743
Ab8	734
Ab9	568
Ab10	542

FIG. 22



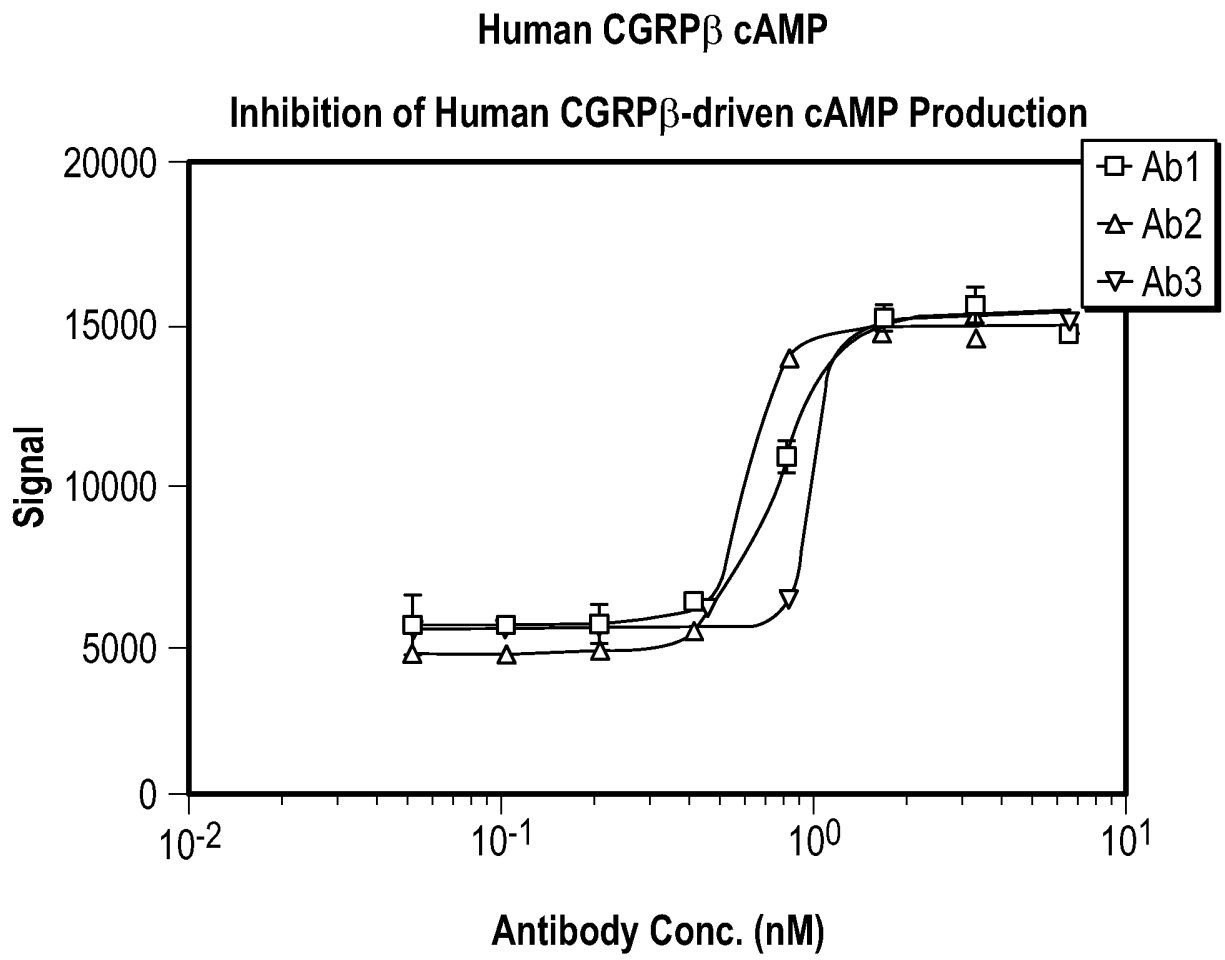
	IC50 (pM)
Ab11	698
Ab12	511
Ab13	498

FIG. 23



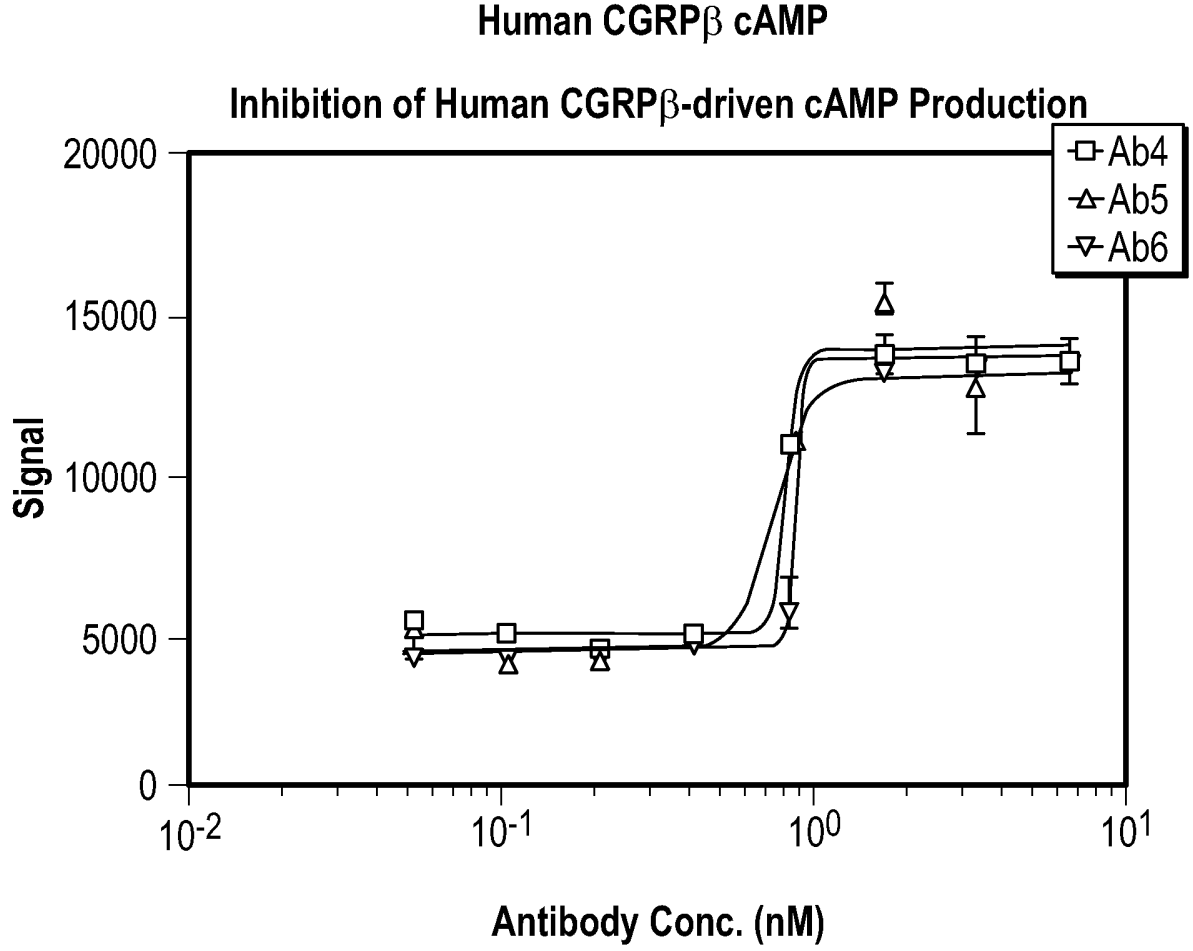
	IC50 (pM)
Ab14	631

FIG. 24



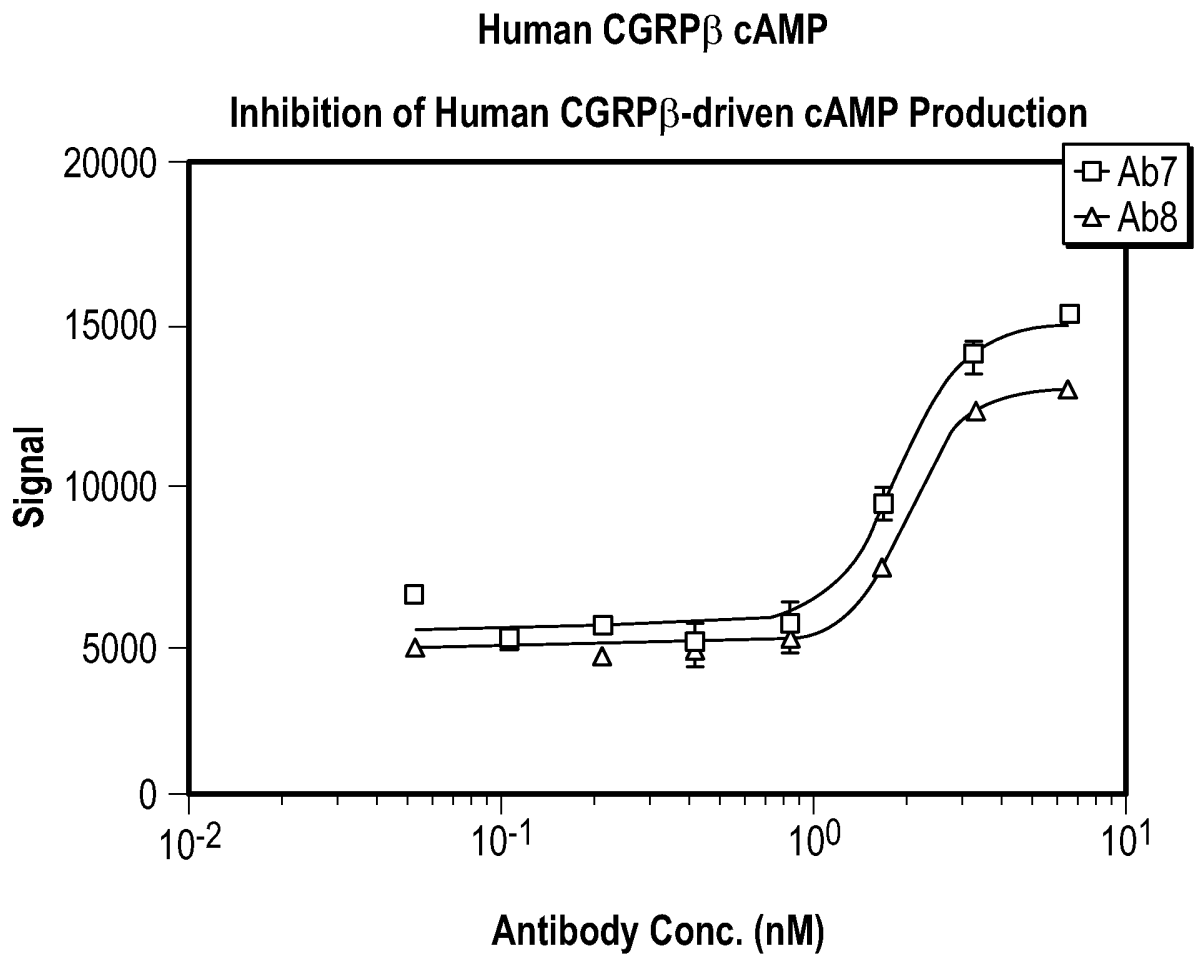
	IC50 (pM)
Ab1	801
Ab2	601
Ab3	989

FIG. 25



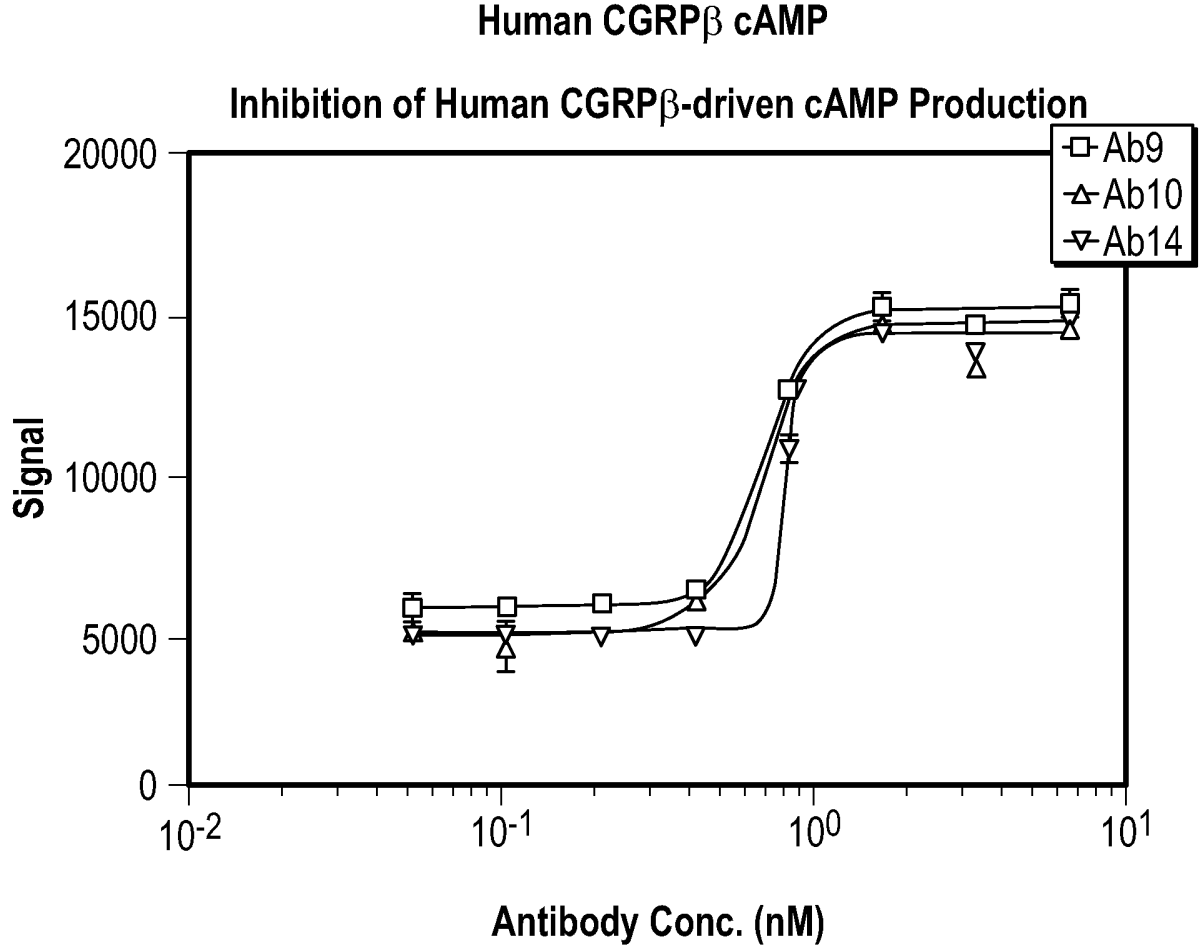
	IC50 (pM)
Ab4	805
Ab5	875
Ab6	740

FIG. 26



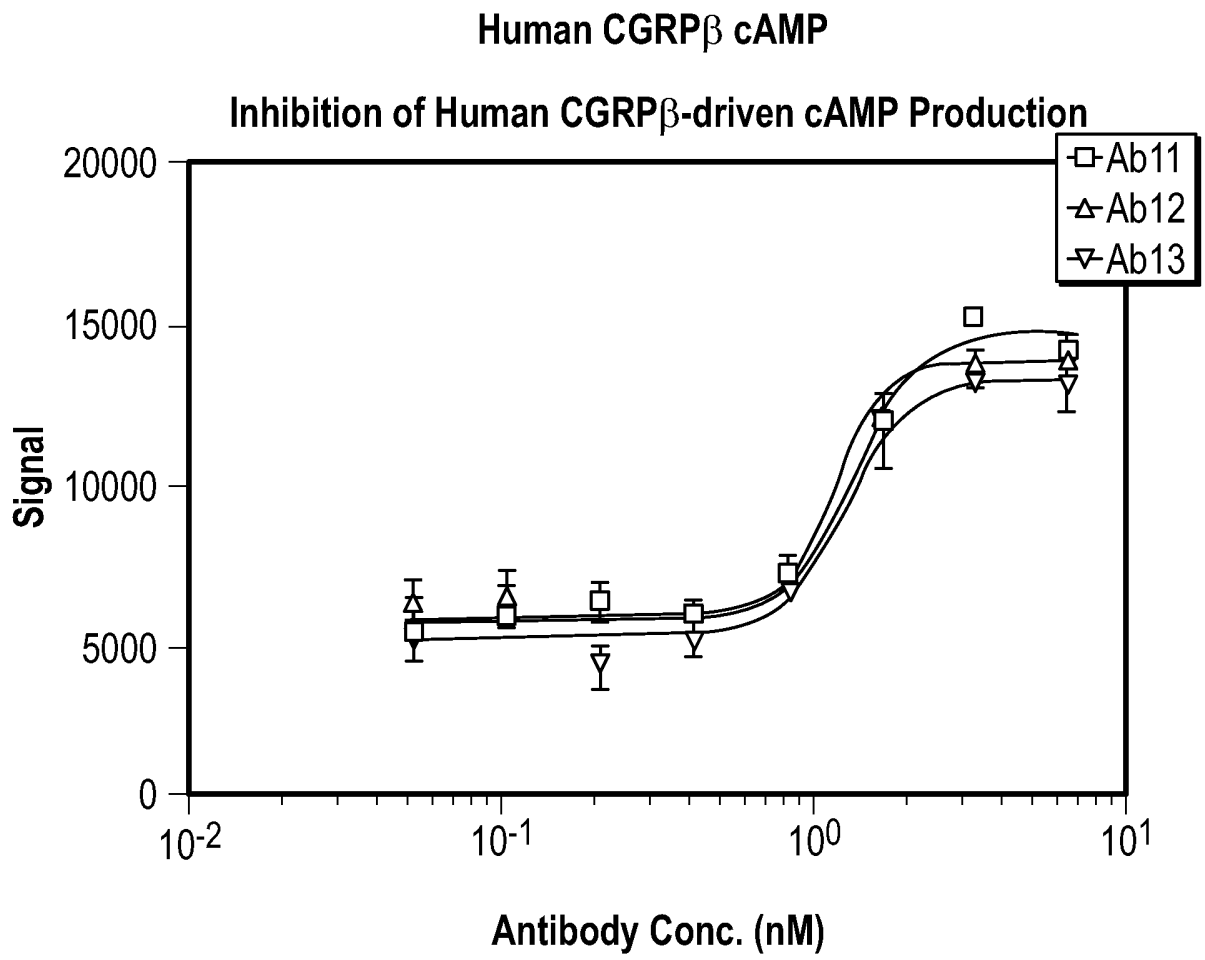
	IC50 (pM)
Ab7	1858
Ab8	1981

FIG. 27



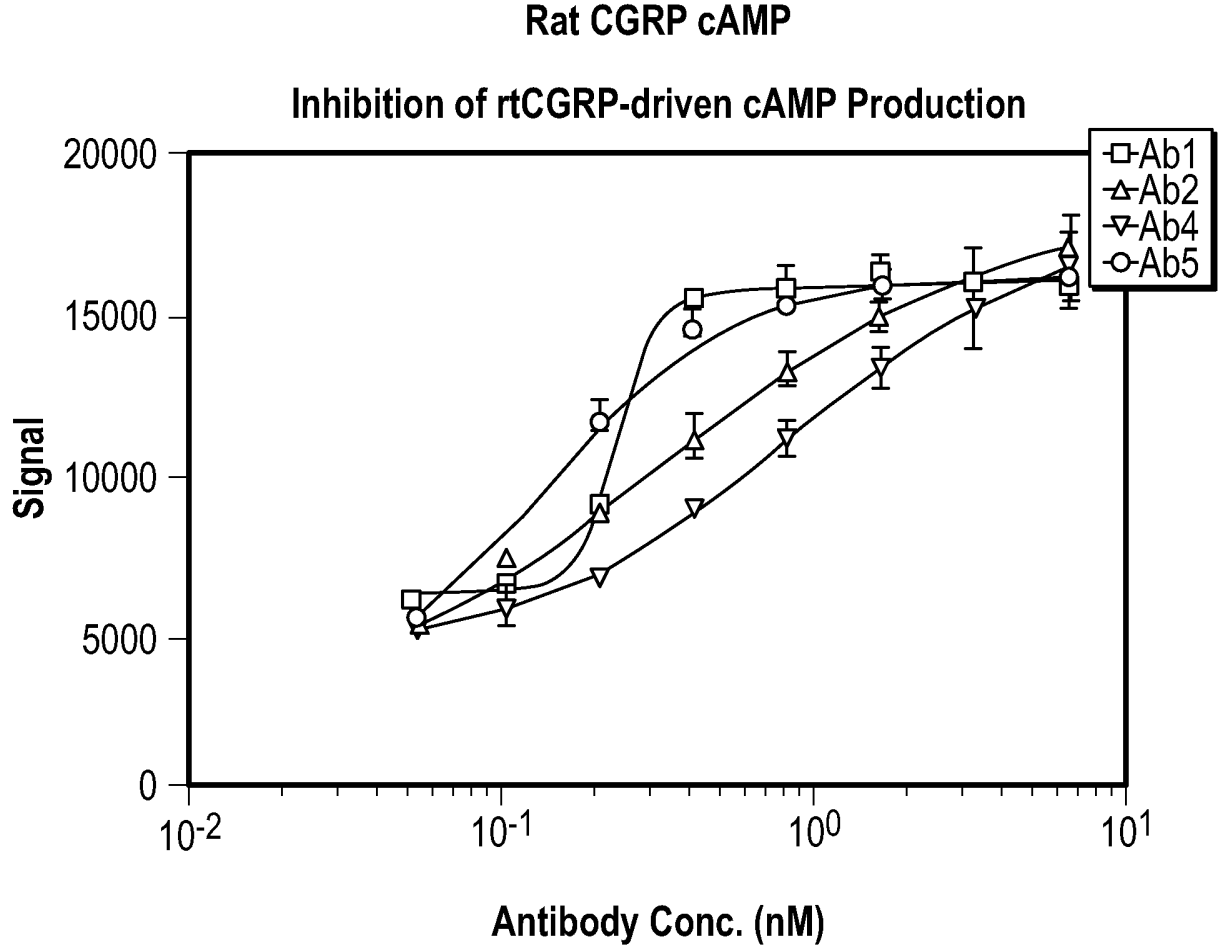
	IC50 (pM)
Ab9	716
Ab10	641
Ab14	812

FIG. 28



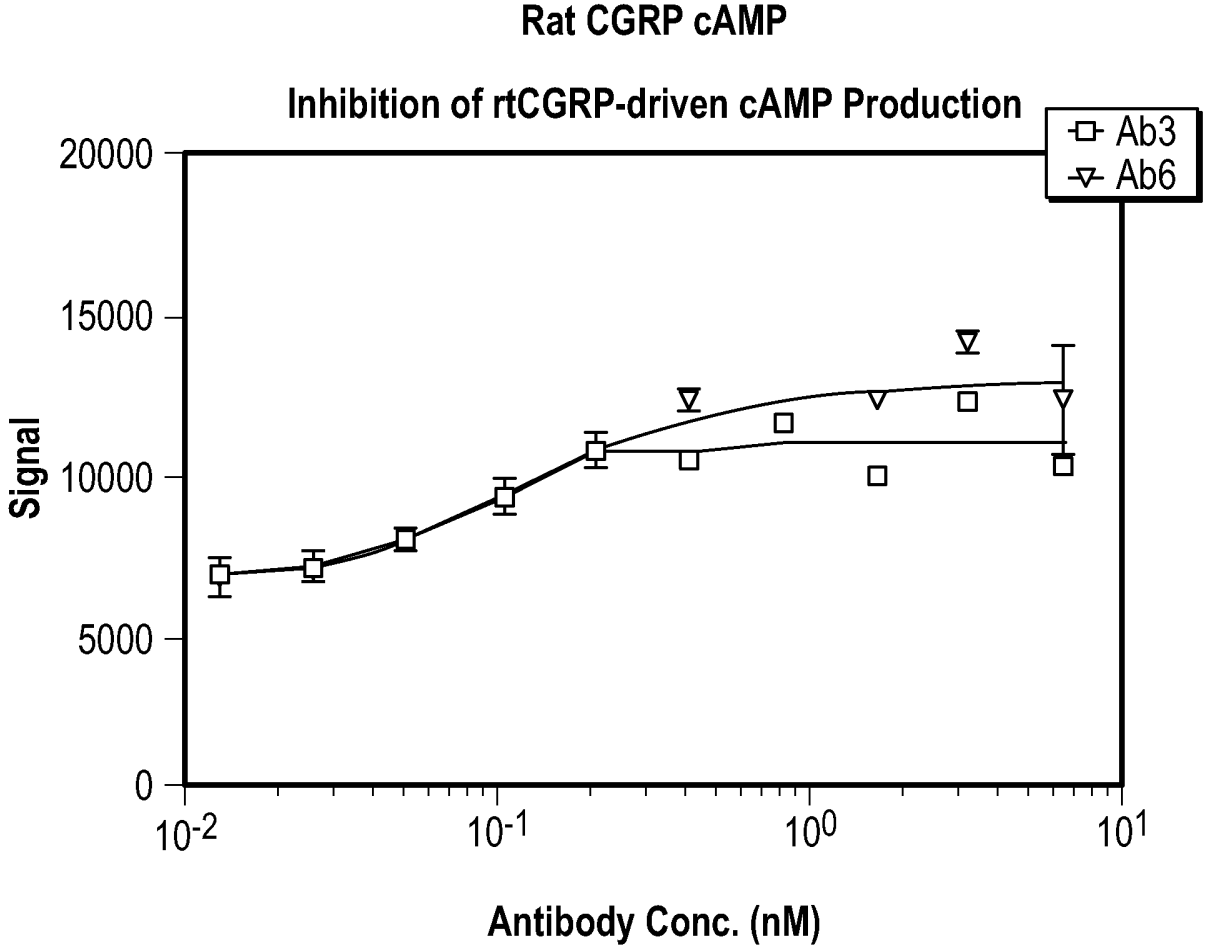
	IC50 (pM)
Ab11	1344
Ab12	1181
Ab13	1276

FIG. 29



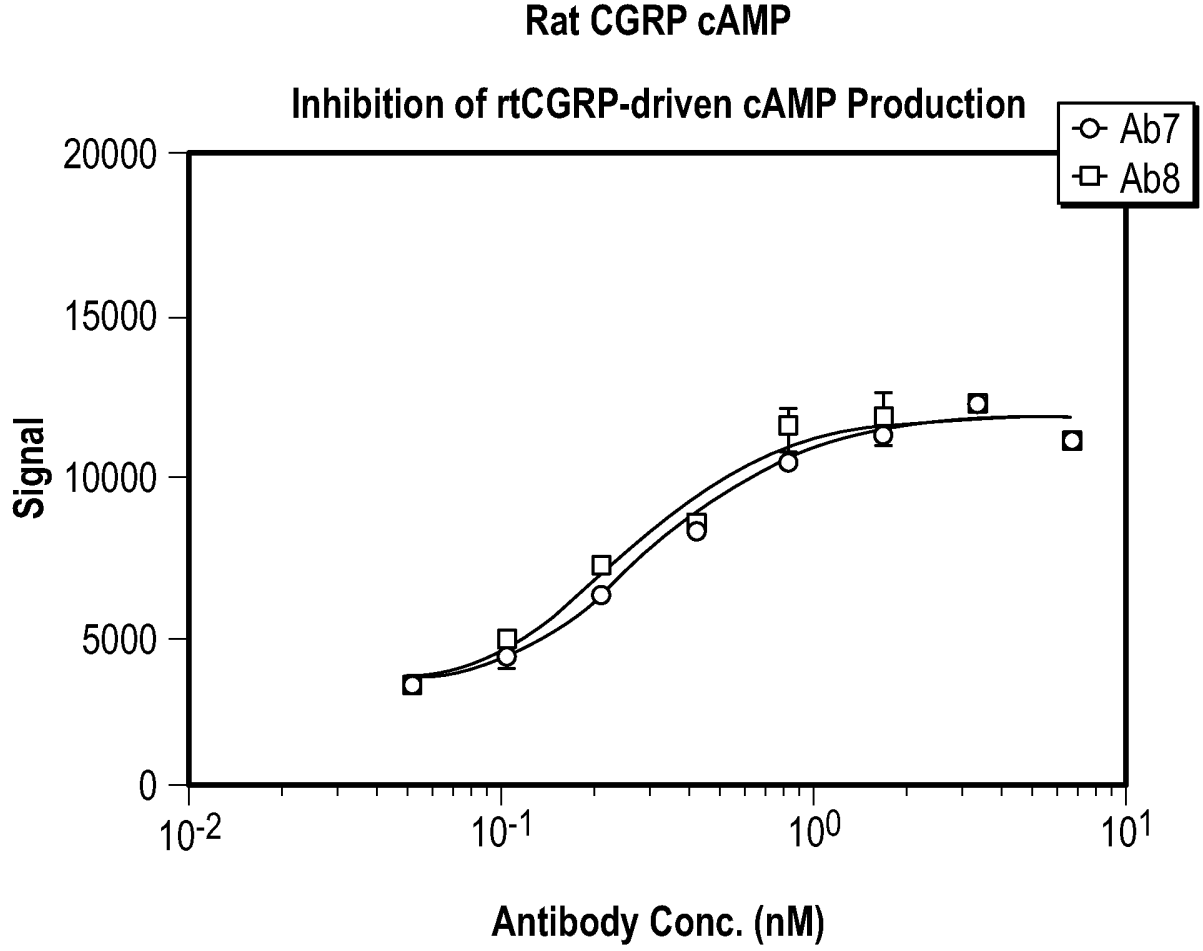
	IC50 (pM)
Ab1	239
Ab2	142
Ab4	868
Ab5	334

FIG. 30



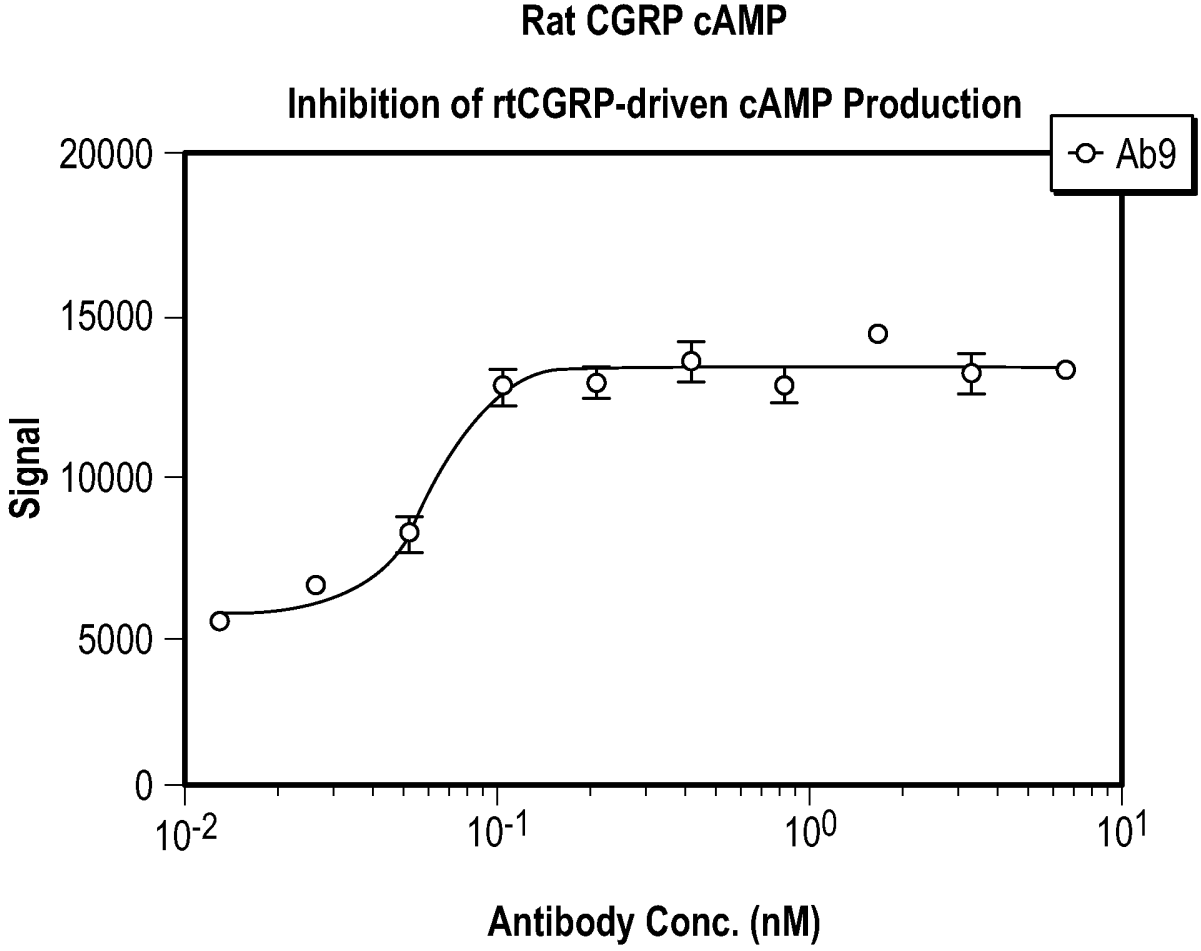
	IC50 (pM)
Ab3	85
Ab6	111

FIG. 31



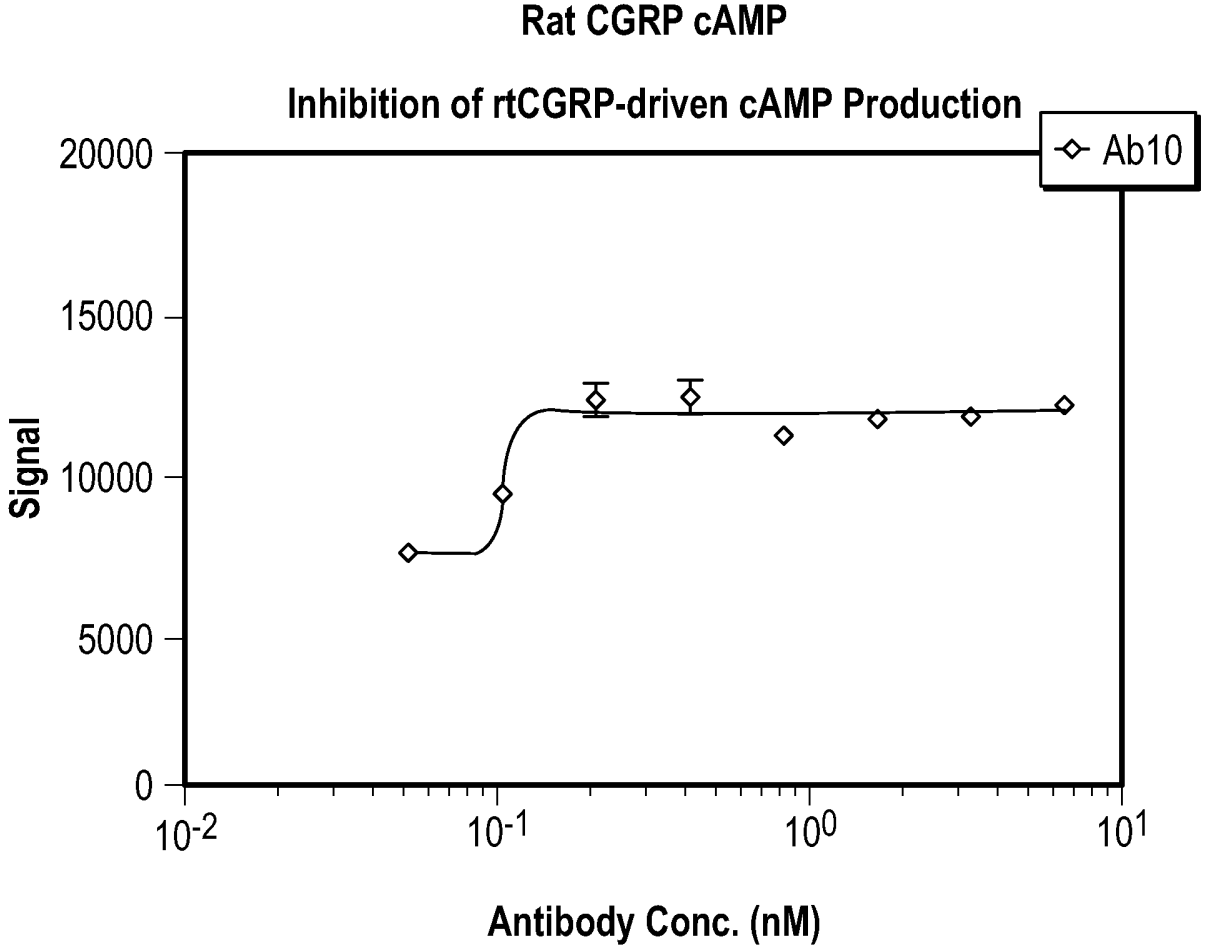
	IC50 (pM)
Ab7	297
Ab8	243

FIG. 32



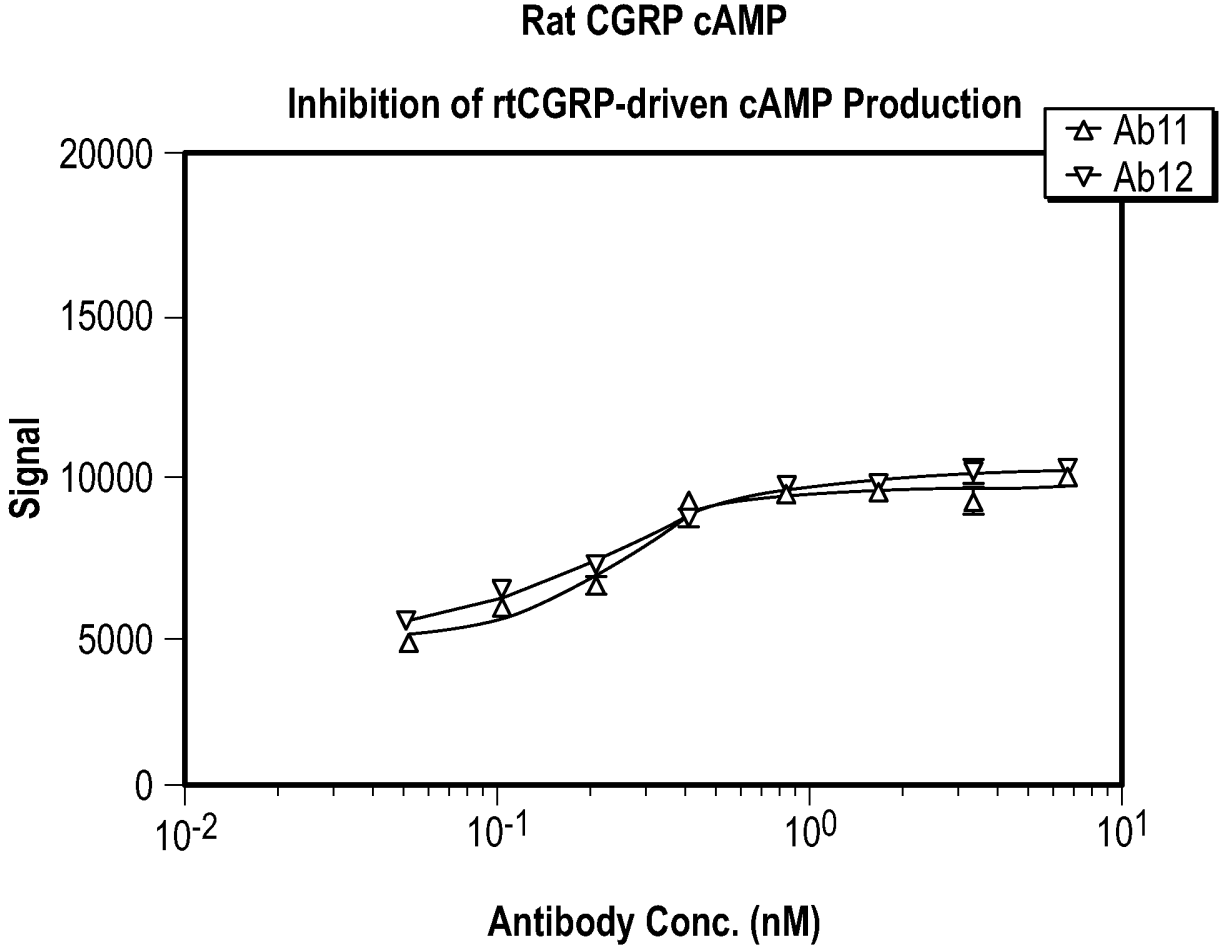
	IC50 (pM)
Ab9	62

FIG. 33



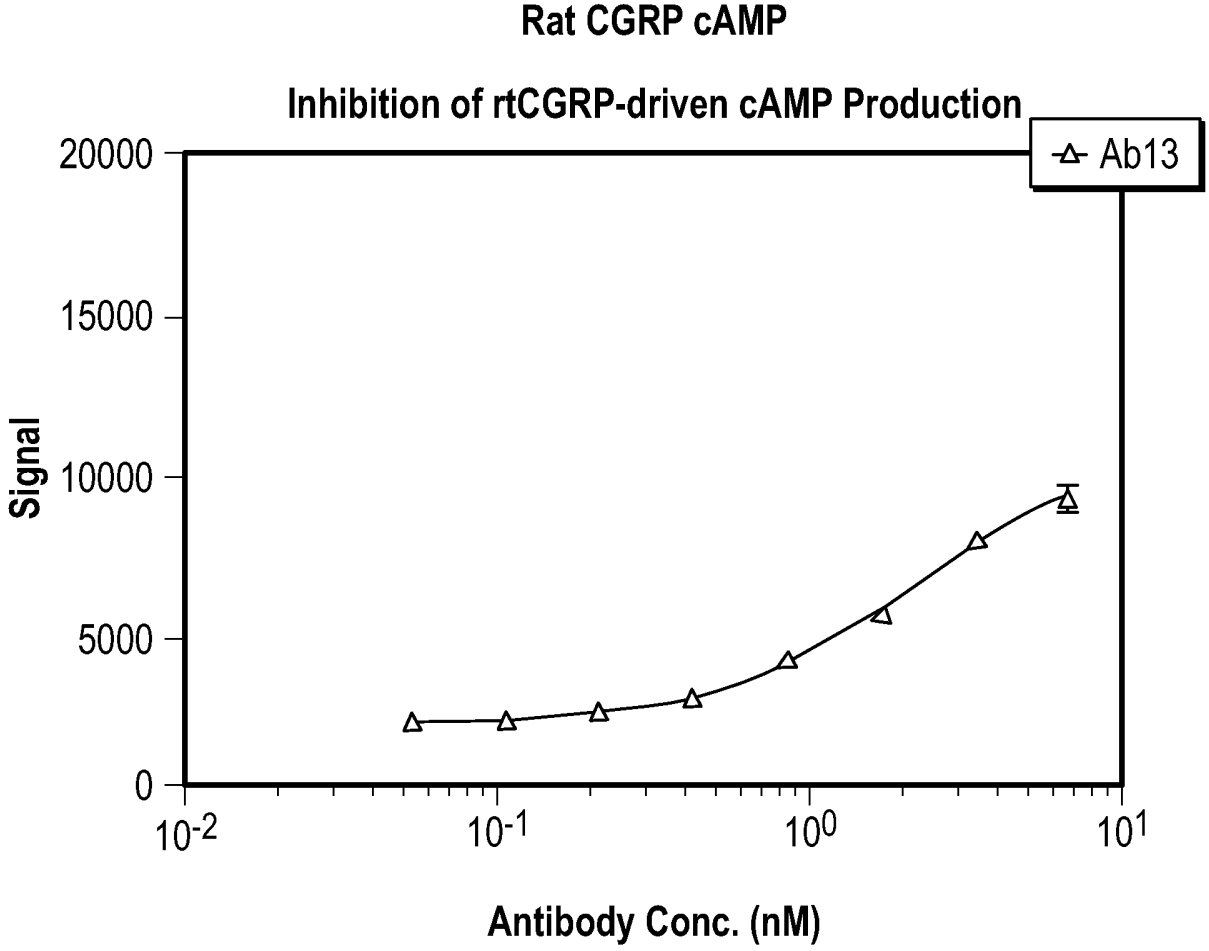
	IC50 (pM)
Ab10	105

FIG. 34



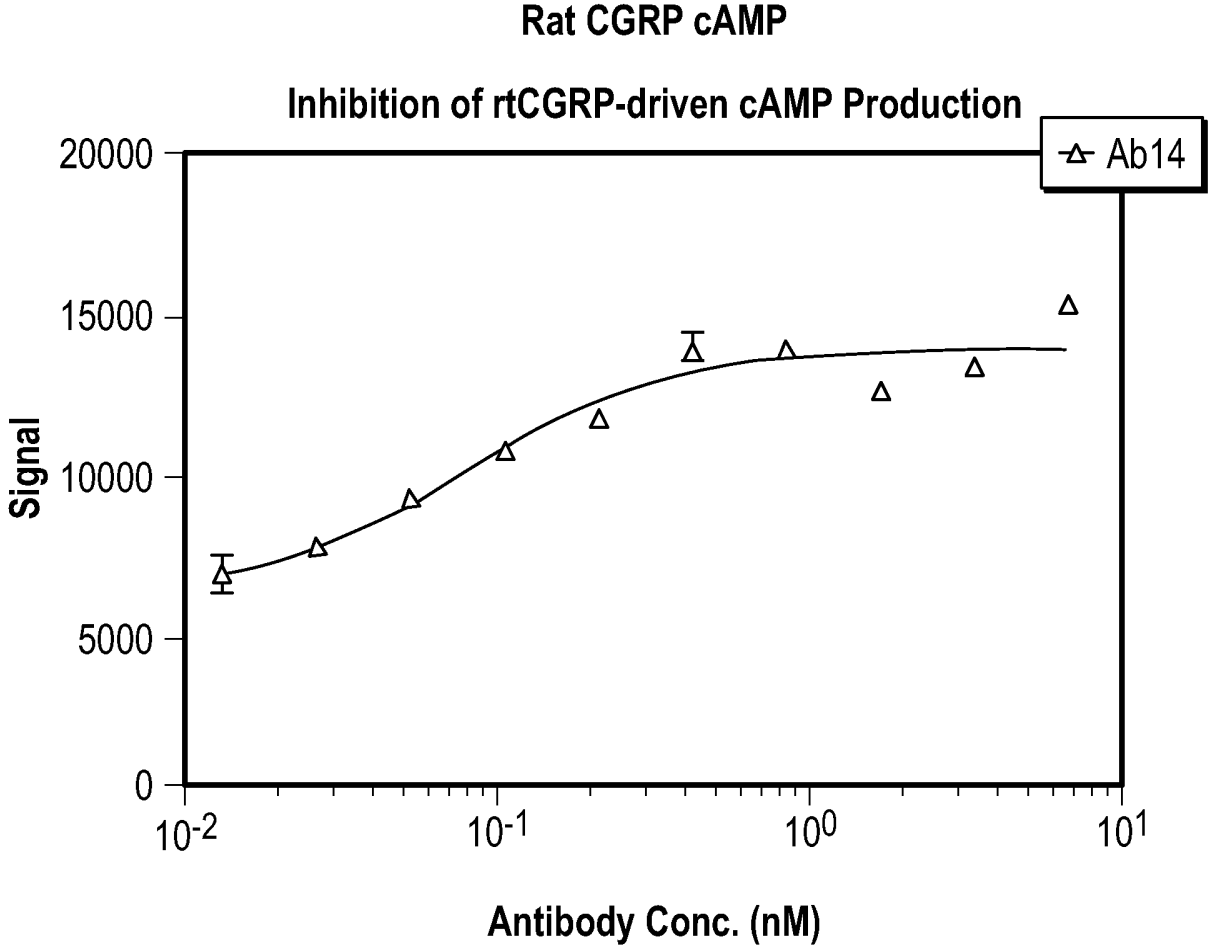
	IC50 (pM)
Ab11	239
Ab12	236

FIG. 35



	IC50 (pM)
Ab13	2036

FIG. 36



	IC50 (pM)
Ab14	81

FIG. 37

Inhibition of Radioligand Binding

	IC_{50}(nM)	K_I(nM)
Ab1	0.585	0.46
Ab2	0.482	0.378
Ab3	2.49	10.96
Ab4	0.579	0.455
Ab5	0.586	0.461
Ab6	2.46	1.94
Ab7	4.53	3.56
Ab8	0.936	0.736
Ab9	2.03	1.6
Ab10	0.28	0.22
Ab11	2.26	1.78
Ab12	0.315	0.248
Ab13	0.335	0.264

FIG. 38

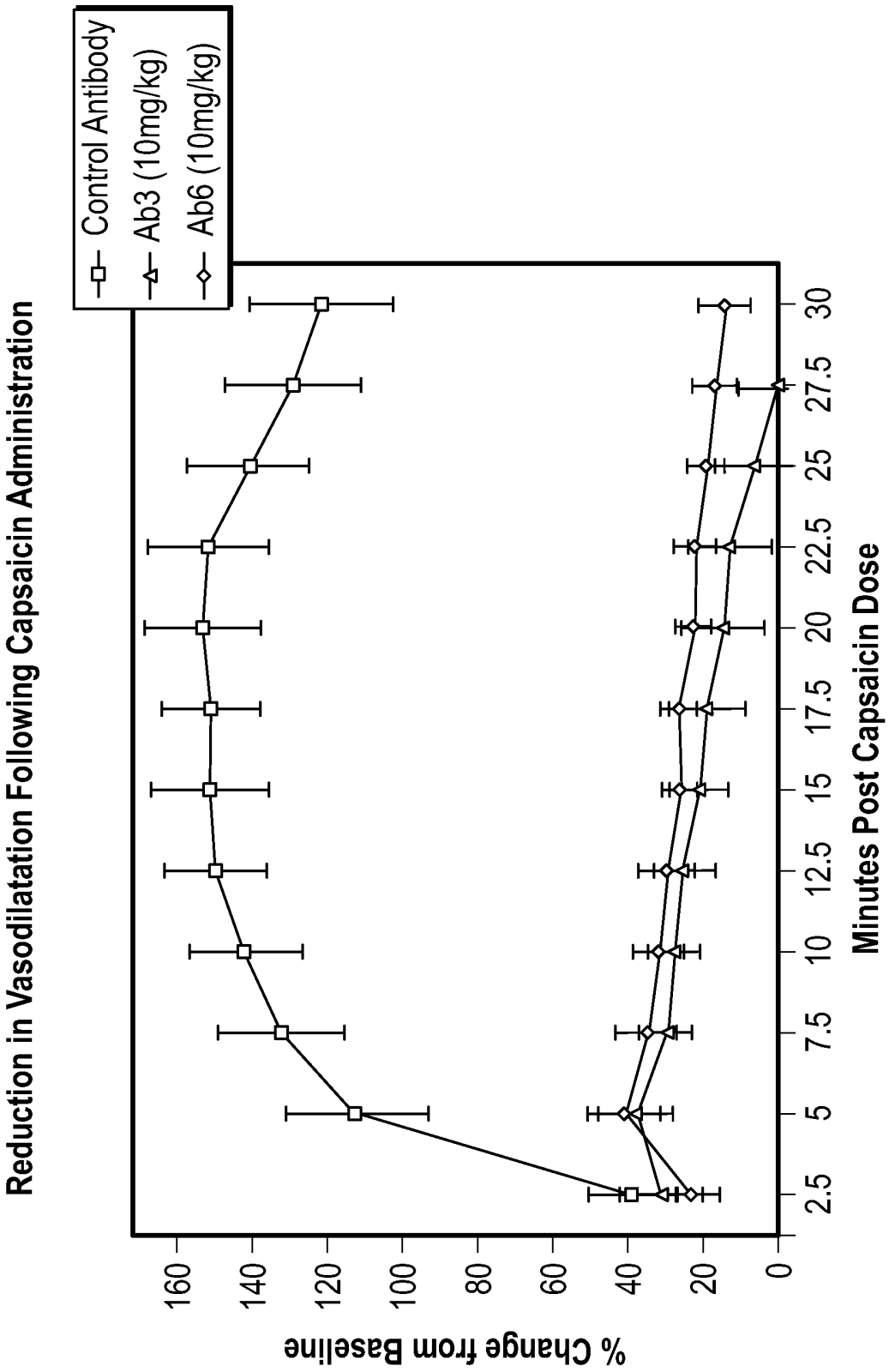

Reduction in Vasodilatation Following Capsaicin Administration
Control Antibody
Ab3 (10mg/kg)
Ab6 (10mg/kg)
% Change from Baseline
0
20
40
60
80
100
120
140
160
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
Minutes Post Capsaicin Dose

FIG. 39

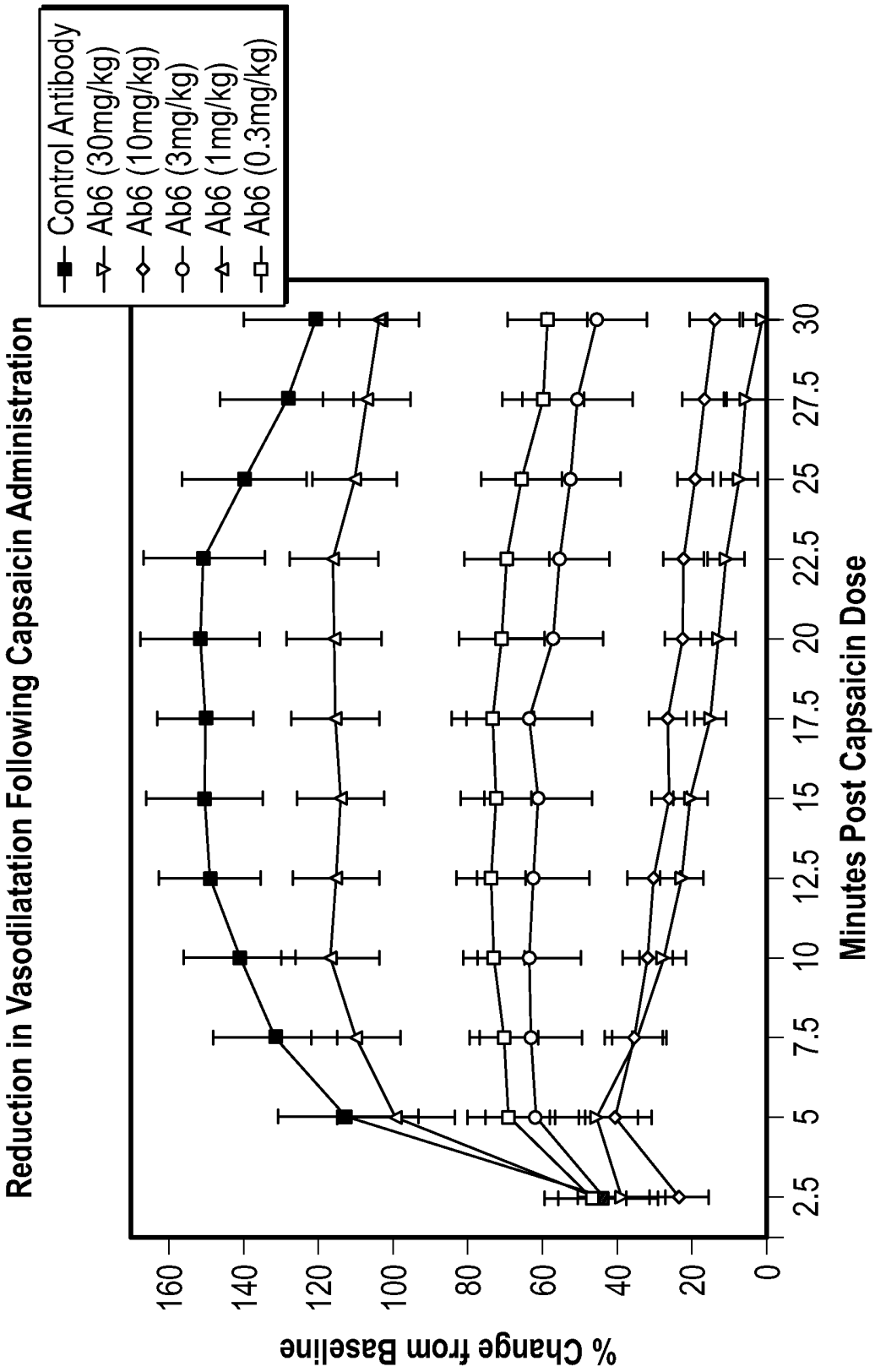

Reduction in Vasodilatation Following Capsaicin Administration
Control Antibody
Ab6 (30mg/kg)
Ab6 (10mg/kg)
Ab6 (3mg/kg)
Ab6 (1mg/kg)
Ab6 (0.3mg/kg)
% Change from Baseline
0
20
40
60
80
100
120
140
160
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
Minutes Post Capsaicin Dose

FIG. 40

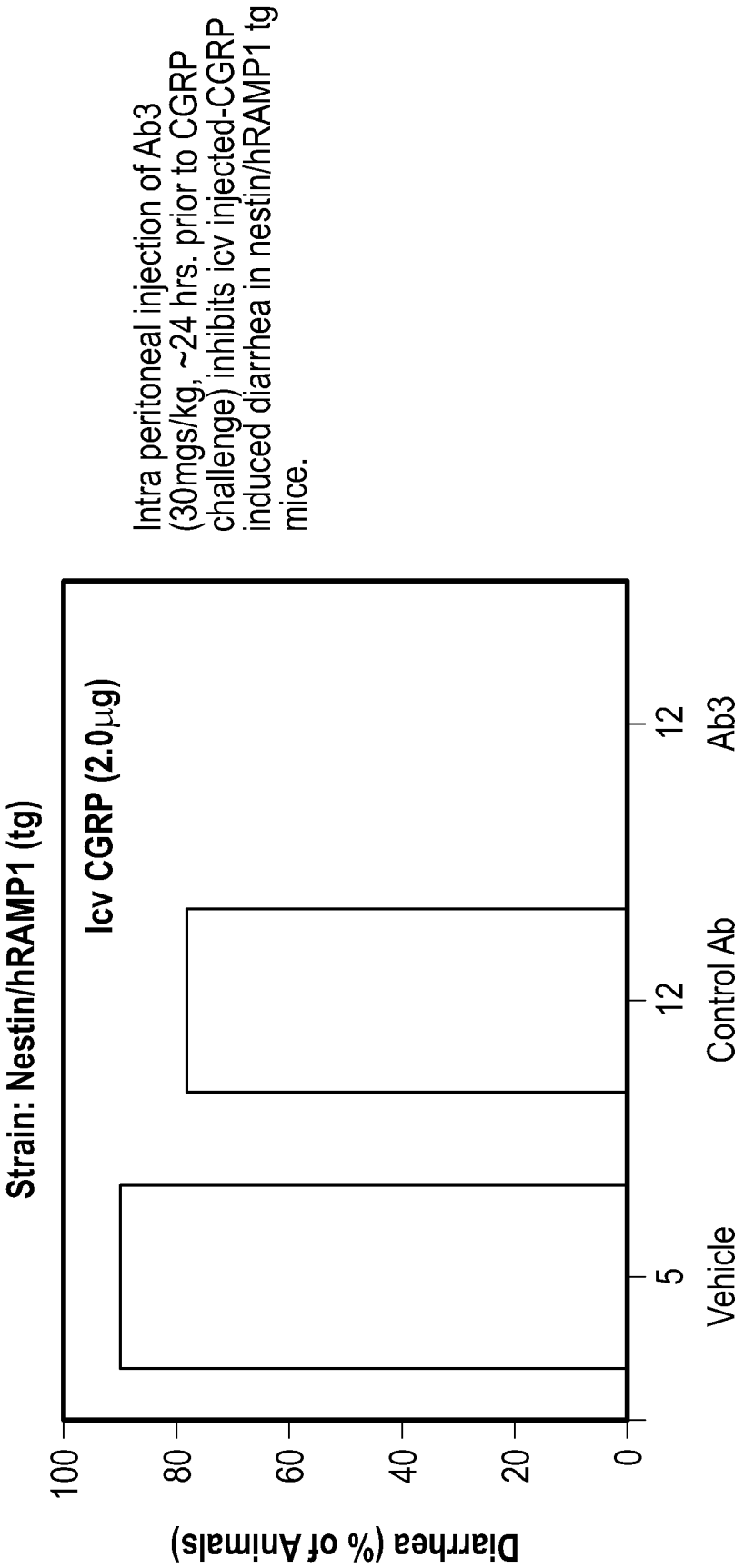

Intra peritoneal injection of Ab3 (30mgs/kg, ~24 hrs. prior to CGRP challenge) inhibits icv injected-CGRP induced diarrhea in nestin/hRAMP1 tg mice.
Strain: Nestin/hRAMP1 (tg)
Icv CGRP (2.0µg)
Diarrhea (% of Animals)
100
80
60
40
20
0
5
12
12
Vehicle
Control Ab
Ab3

FIG. 41

Intra cerebroventricular injection of CGRP induces diarrhea in a dose dependent manner in C57BL/6J mice.

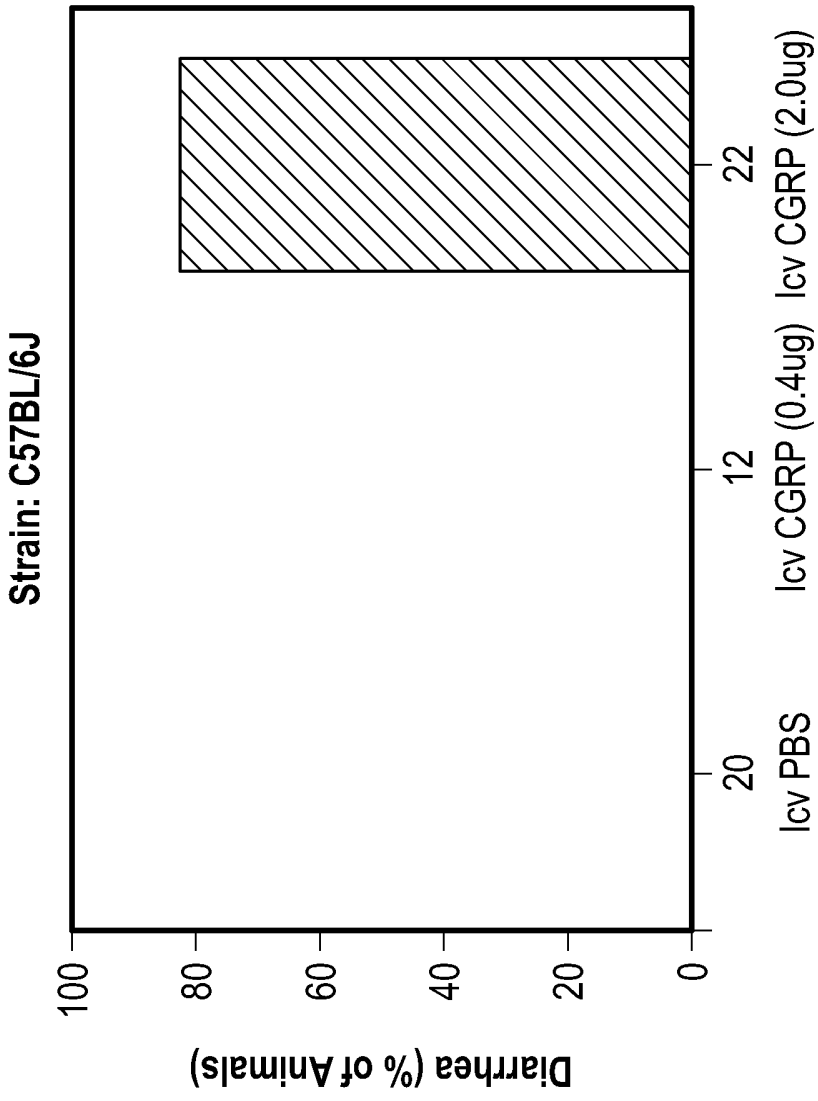


FIG. 42

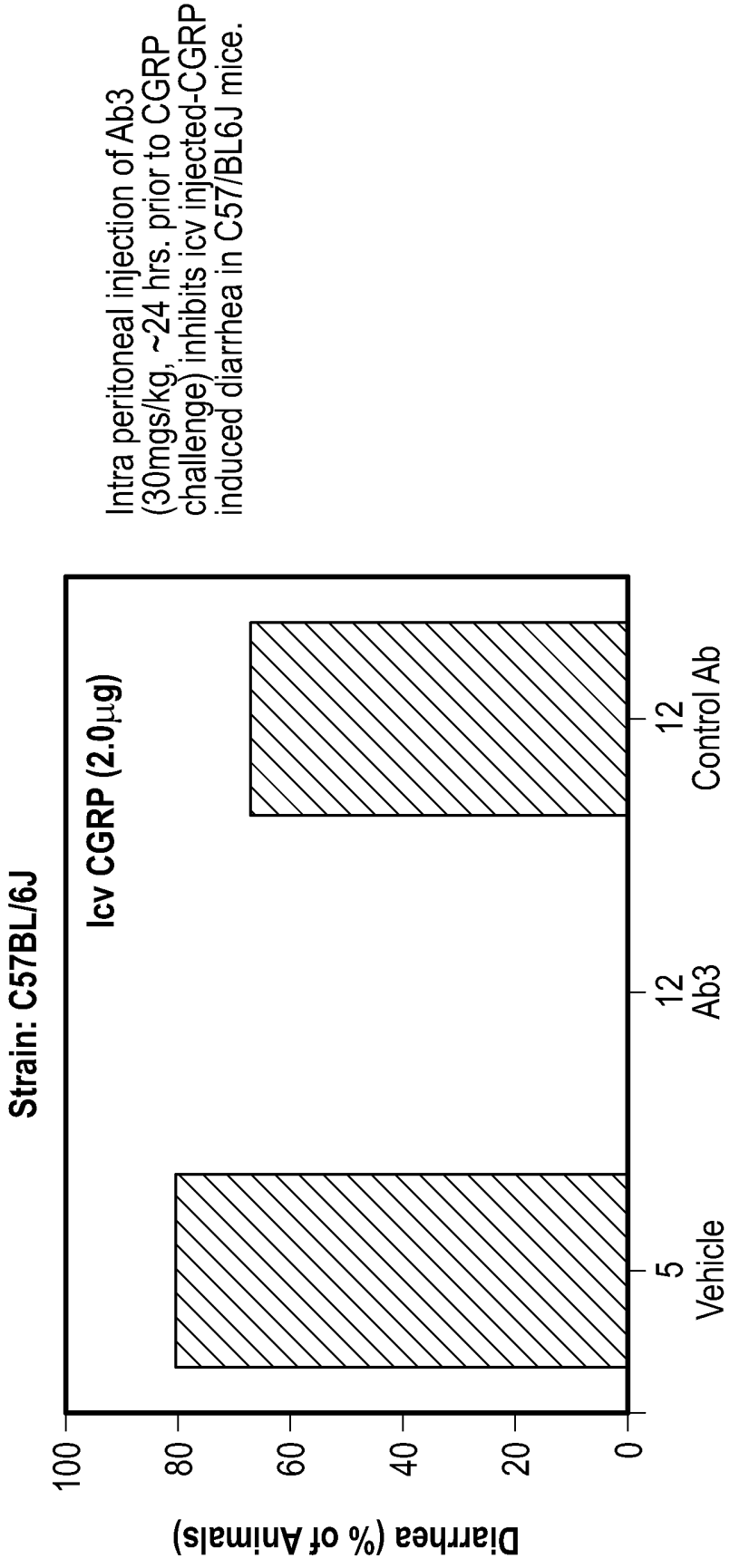

Intra peritoneal injection of Ab3 (30mgs/kg, ~24 hrs. prior to CGRP challenge) inhibits icv injected-CGRP induced diarrhea in C57/BL6J mice.
Strain: C57BL/6J
Icv CGRP (2.0μg)
Diarrhea (% of Animals)
100
80
60
40
20
0
5
Vehicle
12
Ab3
12
Control Ab

FIG. 43

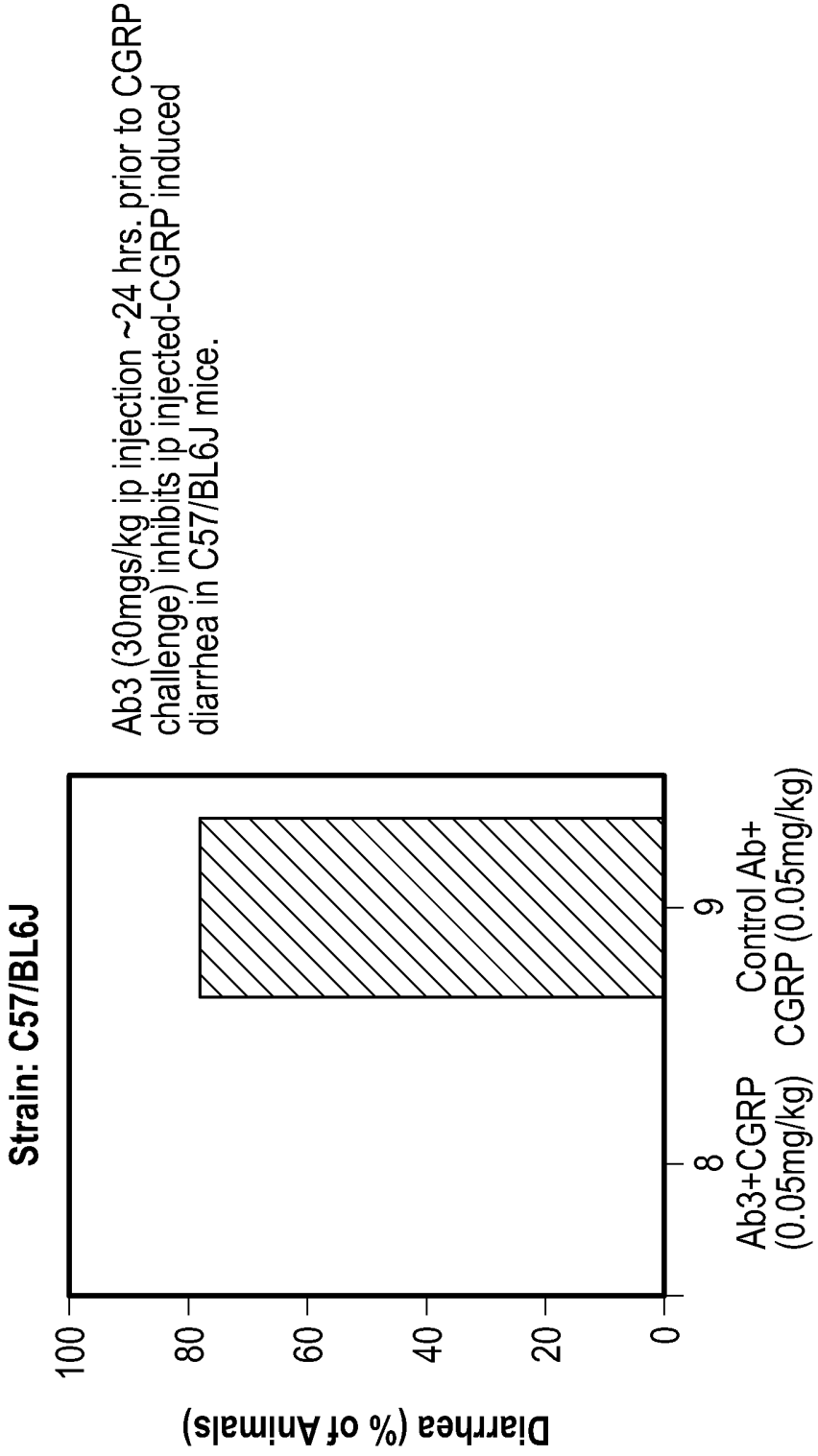

Ab3 (30mgs/kg ip injection ~24 hrs. prior to CGRP challenge) inhibits ip injected-CGRP induced diarrhea in C57/BL6J mice.
Strain: C57/BL6J
Diarrhea (% of Animals)
100
80
60
40
20
0
8
9
Ab3+CGRP (0.05mg/kg)
Control Ab+ CGRP (0.05mg/kg)

FIG. 44

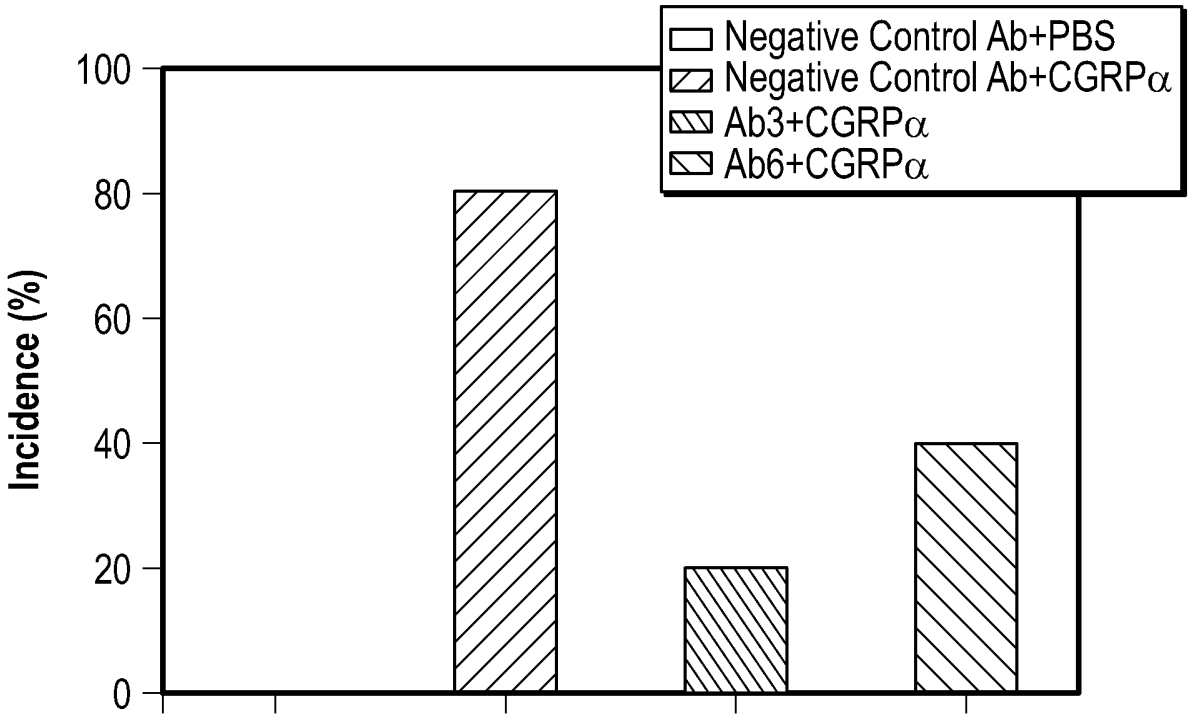

Negative Control Ab+PBS
Negative Control Ab+CGRPα
Ab3+CGRPα
Ab6+CGRPα
Incidence (%)
100
80
60
40
20
0

FIG. 45

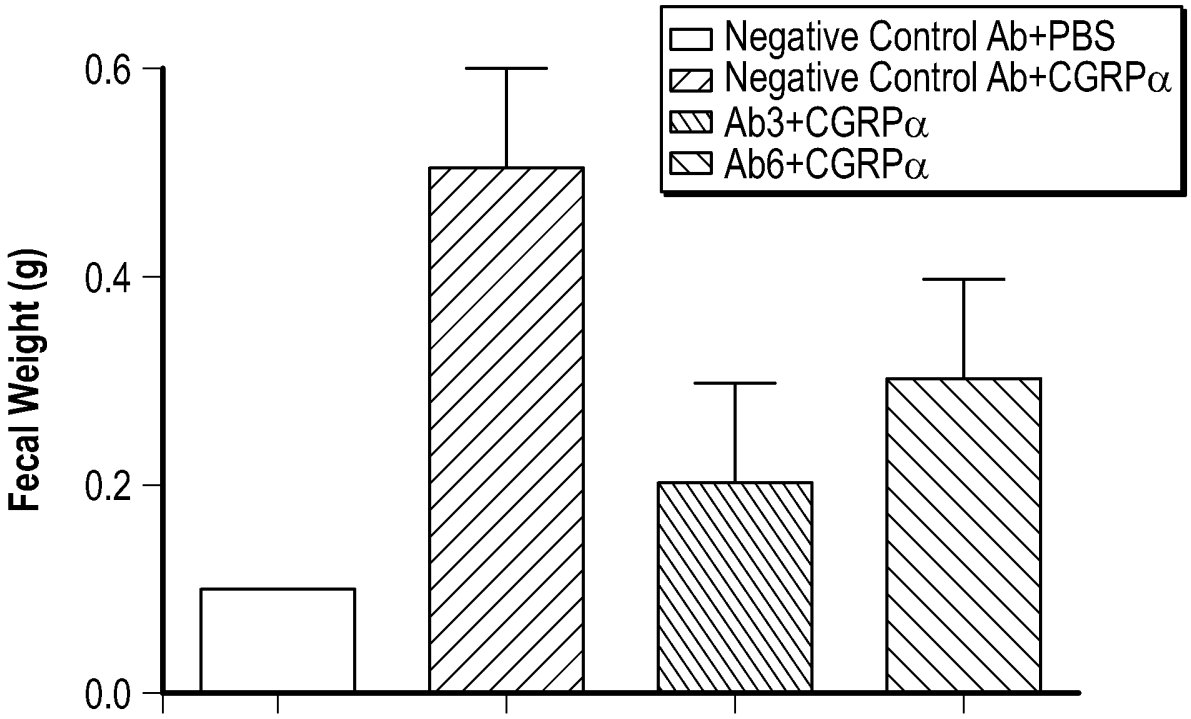

Negative Control Ab+PBS
Negative Control Ab+CGRPα
Ab3+CGRPα
Ab6+CGRPα
Fecal Weight (g)
0.6
0.4
0.2
0.0

FIG. 46

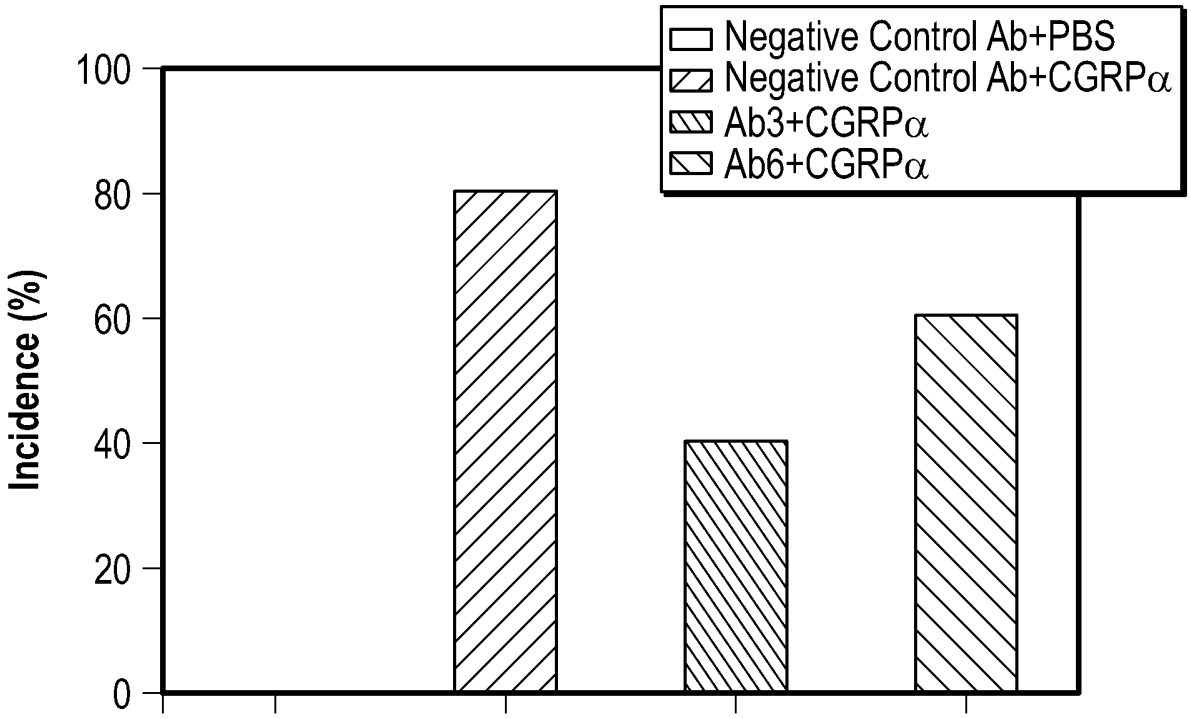

Negative Control Ab+PBS
Negative Control Ab+CGRPα
Ab3+CGRPα
Ab6+CGRPα
Incidence (%)
100
80
60
40
20
0

FIG. 47

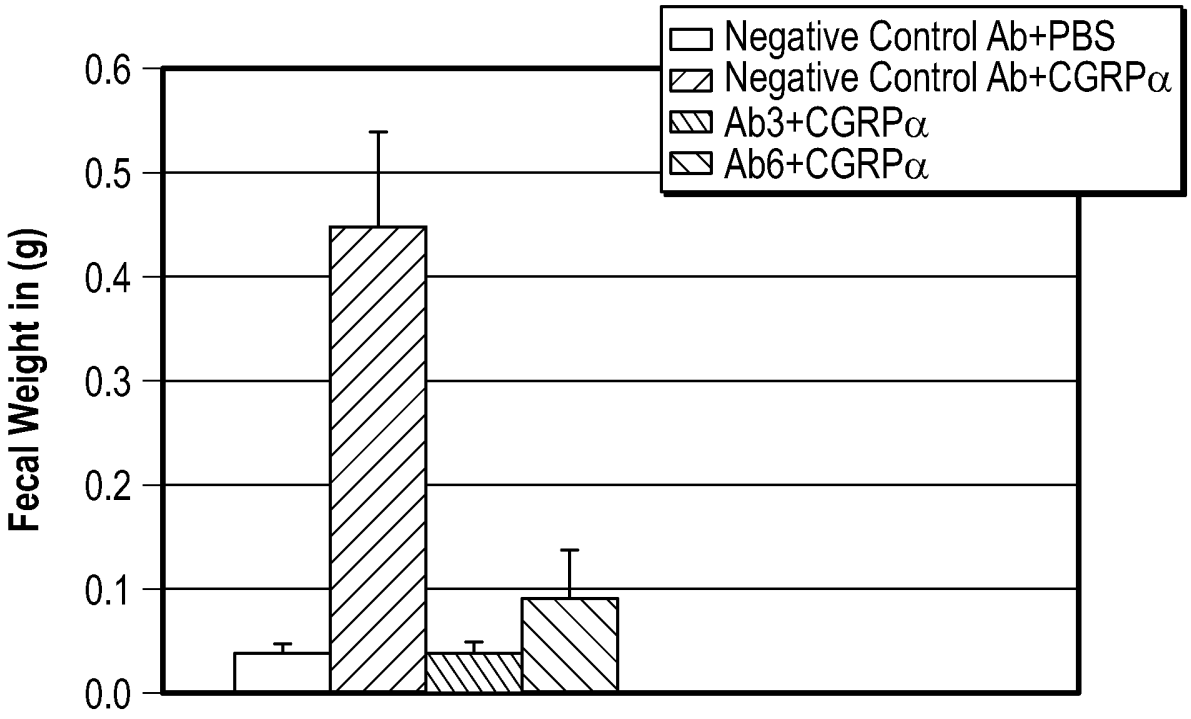

Negative Control Ab+PBS
Negative Control Ab+CGRPα
Ab3+CGRPα
Ab6+CGRPα
Fecal Weight in (g)
0.6
0.5
0.4
0.3
0.2
0.1
0.0

FIG. 48

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13*ter*.1(c) and (d) and 39)

Applicant's or agent's file reference	**IMPORTANT DECLARATION**	Date of mailing (*day/month/year*)
67858-730306		31 OCTOBER 2012 (31.10.2012)
International application No.	International filing date (*day/month/year*)	(Earlist) Priority date *(day/month/year)*
PCT/US2012/038869	**21 MAY 2012 (21.05.2012)**	20 MAY 2011 (20.05.2011)

International Patent Classification (IPC) or both national classification and IPC

A61K 39/395(2006.01)i, A61K 48/00(2006.01)i, A61K 38/16(2006.01)i, A61K 31/7088(2006.01)i, A61P 1/12(2006.01)i

Applicant

ALDERBIO HOLDINGS LLC et al

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. ☒ The subject matter of the international application relates to:
   - a. ☐ scientific theories.
   - b. ☐ mathematical theories.
   - c. ☐ plant varieties.
   - d. ☐ animal varieties.
   - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. ☐ schemes, rules or methods of doing business.
   - g. ☐ schemes, rules or methods of performing purely mental acts.
   - h. ☐ schemes, rules or methods of playing games.
   - i. ☒ methods for treatment of the human body by surgery or therapy.
   - j. ☐ methods for treatment of the animal body by surgery or therapy.
   - k. ☐ diagnostic methods practised on the human or animal body.
   - l. ☐ mere presentation of information.
   - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art.
2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

   ☐ the description ☒ the claims ☐ the drawings

3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:
   - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b)

4. Further coments:

Name and mailing address of ISA/KR

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