ANTI-CGRP COMPOSITIONS AND USE THEREOF

This application claims the benefit of U.S. Provisional Application No. 61/488,660 (Atty. Docket No. 67858.730300) filed May 20, 2011, entitled "ANTI-CGRP COMPOSITIONS AND USE THEREOF" which is hereby incorporated by reference in its entirety.

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 67858o730301.txt and is 203,815 bytes in size.

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention pertains to antibodies and fragments thereof (including Fab fragments) having binding specificity to human Calcitonin Gene Related Peptide (hereinafter "CGRP"). The invention also pertains to methods of screening for diseases and disorders associated with CGRP, and methods of preventing or treating diseases and disorders associated with CGRP by administering said antibodies or fragments thereof.

Description of Related Art

[0002] 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).

[0003] 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).

[0004] 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).

[0005] 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.

[0006] 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, impaired mental

functioning, and addiction. Therefore, it is desirable to identify alternative treatments for pain in order to avoid certain of these negative consequences.

[0007] CGRP is believed to play a role in a multitude of diseases and disorders, including but not limited to migraines, headaches, and pain.

[0008] For example, CGRP reportedly may correlate to or even pay a causal play a role in overactive bladder. Evidence that CGRP may correlate to overactive bladder condition includes the fact that CGRP is present in urinary tract, DRG and spinal cord - (Wharton et al., 1986 Neurosci (3):727) and also that C-fiber afferents are critical for carrying impulses involved in micturition to spinal cord (Yoshida et al., 2011 J Pharmacol Sci (112):128). Further, it has been reported that the intravesical administration of Botox suppresses CGRP and significantly reduces intercontraction interval in acetic acid - induced bladder pain model (Chuang et al., 2004 J Urol (172):1529; Chuang et al., 2009 J Urol (182):786)

[0009] Evidence that CGRP may play a causal role in this condition is a recent published patent application containing data purportedly suggesting that an anti-CGRP Ab disclosed therein reduced the number of bladder contractions in a turpentine-oil – induced overactive bladder model –(Pfizer WO 2011/024113)).

[00010] Due to the perceived involvement of CGRP in these and other 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 remains a need in the art for compositions or methods that reduce or inhibit diseases or disorders associated with CGRP, such as migraines, headaches, overactive bladder, and pain.

BRIEF SUMMARY OF THE INVENTION

[00011] The present invention is directed to 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. Another embodiment of this invention relates to 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").

[00012] In another preferred embodiment of the invention, full length antibodies and Fab fragments thereof are contemplated 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.

[0010] 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 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. The antibodies and antibody fragments of the present invention particularly have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: overactive bladder and other urinary conditions including bladder infection, pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; post-surgical pain, trauma related pain, burn related pain, diabetes; non-insulin dependent diabetes mellitus and other inflammatory autoimmune disorders, vascular disorders; inflammation; arthritis; bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases including pruritis, neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; dysmenorrhea, and other conditions that potentially may be treated or prevented or the symptoms ameliorated by antagonism of CGRP receptors. Of

particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache, and other pain related conditions as well as overactive bladder.

[0011] In another embodiment of the invention, chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP are preferably useful in methods directed to reducing, treating, or preventing gastro-esophageal reflux, 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.

[0012] In another embodiment of the invention these antibodies and humanized versions 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.

[0013] The invention also contemplates conjugates of anti-CGRP antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates methods of making said chimeric or humanized anti-CGRP or anti-CGRP/CGRP-R complex antibodies and binding fragments thereof. 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.

[0014] 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. 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. 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

[0015] Figure 1 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab1.

[0016] Figure 2 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab2.

[0017] Figure 3 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab3.

[0018] Figure 4 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab4.

[0019] Figure 5 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab5.

[0020] Figure 6 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab6.

[0021] Figure 7 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab7.

[0022] Figure 8 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab8.

[0023] Figure 9 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab9.

[0024] Figure 10 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab10.

[0025] Figure 11 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab11.

[0026] Figure 12 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab12.

[0027] Figure 13 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab13.

[0028] Figure 14 provides polynucleotide and polypeptide sequences corresponding to the full-length Antibody Ab14.

[0029] Figure 15 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 *infra* for antibodies Ab1, Ab2, Ab3, and Ab4.

[0030] Figure 16 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 *infra* for antibodies Ab5, Ab6, Ab7, and Ab8.

[0031] Figure 17 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 *infra* for antibodies Ab9, Ab10, and Ab14.

[0032] Figure 18 provides the CGRP-alpha ELISA binding data obtained following the protocol in Example 1 *infra* for antibodies Ab11, Ab12, and Ab13.

[0033] 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*.

[0034] Figure 20 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibody Ab3, obtained following the protocol in Example 1 *infra*.

[0035] Figure 21 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibodies Ab5 and Ab6, obtained following the protocol in Example 1 *infra*.

[0036] 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*.

[0037] 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*.

[0038] Figure 24 demonstrates the inhibition of CGRP-alpha-driven cAMP production by antibody Ab14, obtained following the protocol in Example 1 *infra*.

[0039] 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*.

[0040] 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*.

[0041] Figure 27 demonstrates the inhibition of CGRP-beta-driven cAMP production by antibodies Ab7 and Ab8, obtained following the protocol in Example 1 *infra*.

[0042] 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*.

[0043] 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*.

[0044] 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*.

[0045] Figure 31 demonstrates the inhibition of rat CGRP -driven cAMP production by antibodies Ab3 and Ab6, obtained following the protocol in Example 1 *infra*.

[0046] Figure 32 demonstrates the inhibition of rat CGRP-driven cAMP production by antibodies Ab7 and Ab8, obtained following the protocol in Example 1 *infra*.

[0047] Figure 33 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab9, obtained following the protocol in Example 1 *infra*.

[0048] Figure 34 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab10, obtained following the protocol in Example 1 *infra*.

[0049] Figure 35 demonstrates the inhibition of rat CGRP-driven cAMP production by antibodies Ab11 and Ab12, obtained following the protocol in Example 1 *infra*.

[0050] Figure 36 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab13, obtained following the protocol in Example 1 *infra*.

[0051] Figure 37 demonstrates the inhibition of rat CGRP-driven cAMP production by antibody Ab14, obtained following the protocol in Example 1 *infra*.

[0052] 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*.

[0053] 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*.

[0054] 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*.

[0055] FIG. 41A-C shows the beneficial effect of Ab3 on bladder capacity during saline infusion. Animals were administered Ab3 or a negative control antibody, then monitored during infusion of saline into the bladder. ICI (panel A) was increased and MF (panel B) was decreased, indicating increased bladder capacity. Differences in AM (panel C) were within the standard deviation and not statistically significant. Asterisks indicate statistically significant improvement ($p < 0.05$ unpaired Student's t-test, comparison to Negative control Ab). Legend: filled bars: Ab3 treated (10 mg/kg); open bars: negative control antibody (10 mg/kg). Error bars indicate the standard deviation. Abbreviations: ICI : Intercontraction Interval; MF : Micturition Frequency; AM : Amplitude of Micturition.

[0056] FIG. 42 shows the effect Ab2 in a model of neuropathic pain. Mechanical allodynia was induced by Chung surgery (L5/L6 spinal nerve ligation), and degree of sensitivity was compared between Ab2 treated animals (hashed bars) and control animals (filled bars). Higher values indicate less sensitivity. Average sensitivity was similar at day 13 (prior to Ab2 administration) but improved at days 14 and 17. Error bars indicate the standard error of the mean.

[0057] FIG. 43 shows the analgesic effect of Ab2 and morphine. Pain sensitivity was assessed by the tail withdrawal time (y-axis, seconds) for animals administered morphine (open squares), Ab2 (10 mg/kg, filled triangles), or vehicle (negative control, open circles). Animals developed morphine tolerance and exhibited tail withdrawal times similar to control animals by day 4. In contrast, Ab2-treated animals exhibited a sustained improvement in tail withdrawal time over the course of the experiment (to day 7). The improvement in Ab2-treated animals was statistically significant ($p < 0.05$ one-way ANOVA followed by Dunnett's test, comparison to vehicle, indicated by asterisks). Error bars indicate the standard error of the mean.

[0058] FIG. 44 shows the dosage-dependent analgesic effect of Ab2. On day 0 (subsequent to the first tail withdrawal time test), rats were administered antibody Ab2 at a dosage of 1 mg/kg (filled squares), 3 mg/kg (filled downward-pointing triangles), or 10 mg/kg (filled upward-pointing triangles), or a vehicle (open circles) or negative control antibody (open squares). The rats' tail withdrawal time in response to a painful thermal stimulus was assessed daily (higher times indicate relative insensitivity to pain). Tail withdrawal time was increased in a dosage-dependent manner by the administration of Ab2. Asterisks indicate statistically significant increases in tail withdrawal time ($p < 0.05$ one-way ANOVA followed by Dunnett's test, comparison to vehicle). Error bars indicate the standard error of the mean.

[0059] FIG. 45 shows the analgesic effect of Ab2 in combination with morphine, and when morphine is withdrawn after the onset of morphine tolerance. On day 0 (subsequent to the first tail withdrawal time test), rats were administered antibody Ab2 at a dosage of 10 mg/kg (filled squares and filled triangles) or vehicle (open circles). The rats were then daily administered morphine on days 1 to 10 (filled squares) or only on days 1 to 4 (filled triangles). The tail withdrawal time initially was greatly increased in the morphine-treated mice, but decreased on subsequent days indicating morphine tolerance. However, in the mice from which morphine was withdrawn after day 4, tail withdrawal time increased and remained elevated between days 5 and 8. Error bars indicate the standard error of the mean.

[0060] FIG. 46 shows the effect of Ab2 in a rat model of visceral pain. Visceral pain was quantified by measuring the colonic distension threshold (higher values indicate less sensitivity) for naïve animals (open bar) or animals treated with TNBS to provoke chronic colonic hypersensitivity which either received a negative control antibody (filled bars) or Ab2 (hashed bars). Hypersensitivity was alleviated by 27% by the Ab2-treated animals, and distension threshold was significantly improved by administration of Ab2 ($p < 0.05$ Student's t-test, comparison to TNBS + Negative control group). Error bars indicate the standard error of the mean.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

[0061] 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.

[0062] *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):

CGRP-alpha: ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF-NH_2 (SEQ ID NO: 281), wherein the N-terminal phenylalanine is amidated;

CGRP-beta: ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-NH_2 (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.

[0063] *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.

[0064] 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*.

[0065] 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*.

[0066] *Haploid Yeast Cell*: A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[0067] *Polyploid Yeast Cell*: A cell having more than one copy of its normal genomic (chromosomal) complement.

[0068] *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.

[0069] *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.

[0100] *Yeast Mating*: The process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

[0101] *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.

[0102] *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.

[0103] *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.

[0104] 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.

[0105] 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.

[0106] 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 (Gateway^{R} Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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).

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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.

[0116] *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.

[0117] *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.*

[0118] 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.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), 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, and IgG4 constant regions.

[0125] 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.

[0126] 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.

[0127] 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*.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] "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.

[0133] 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 F_{ab} region; the stem portion of the "Y" configuration is designated the F_C 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.

[0134] 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.

[0135] 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 (V_H) followed by a

number of constant domains. Each light chain has a variable domain (V_L) 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.

[0136] 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)).

[0137] 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

[0138] In one embodiment, the invention includes chimeric antibodies 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).

[0139] The invention also includes chimeric antibodies 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).

[0140] The invention further includes chimeric antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:
QSLEESGGRLVTPGTPLTLTCTVSGLDLSSYYMQWVRQAPGKGLEWIGVIGINDNT
YYASWAKGRFTISRASSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSS
(SEQ ID NO: 3).

[0141] The invention also includes chimeric antibodies 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).

[0142] The invention further contemplates antibodies 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.

[0143] The invention also contemplates fragments of the antibody 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.

[0144] 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: 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.

[0145] 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: 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.

[0146] The invention also contemplates antibody fragments 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: 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.

[0147] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody 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.

[0148] 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 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.

[0149] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab1. In another embodiment of the invention, anti-CGRP antibodies 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

[0150] In one embodiment, the invention includes humanized antibodies 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).

[0151] The invention also includes humanized antibodies 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).

[0152] The invention further includes humanized antibodies 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).

[0153] The invention also includes humanized antibodies 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).

[0154] The invention further contemplates antibodies 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.

[0155] The invention also contemplates fragments of the antibody 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.

[0156] 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: 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.

[0157] 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: 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.

[0158] The invention also contemplates antibody fragments 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: 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.

[0159] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody 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.

[0160] 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 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.

[0161] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab2. In another embodiment of the invention, anti-CGRP antibodies 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

[0162] In one embodiment, the invention includes humanized antibodies 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).

[0163] The invention also includes humanized antibodies 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).

[0164] The invention further includes humanized antibodies 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).

[0165] The invention also includes humanized antibodies 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).

[0166] The invention further contemplates antibodies 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 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.

[0167] The invention also contemplates fragments of the antibody 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: 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.

[0168] 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.

[0169] 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: 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.

[0170] The invention also contemplates antibody fragments 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.

[0171] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody 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.

[0172] 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 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.

[0173] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab3. In another embodiment of the invention, anti-CGRP antibodies 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

[0174] In one embodiment, the invention includes chimeric antibodies 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).

[0175] The invention also includes chimeric antibodies 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).

[0176] The invention further includes chimeric antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:
QSLEESGGRLVTPGTPLTLTCSVSGIDLSGYYMNWVRQAPGKGLEWIGVIGINGAT
YYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSS
(SEQ ID NO: 33).

[0177] The invention also includes chimeric antibodies 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).

[0178] The invention further contemplates antibodies 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.

[0179] The invention also contemplates fragments of the antibody 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.

[0180] 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: 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.

[0181] 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: 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.

[0182] The invention also contemplates antibody fragments 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.

[0183] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody 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.

[0184] 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 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.

[0185] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab4. In another embodiment of the invention, anti-CGRP antibodies 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*.

Antibody Ab5

[0186] In one embodiment, the invention includes humanized antibodies 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).

[0187] The invention also includes humanized antibodies 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).

[0188] The invention further includes humanized antibodies 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).

[0189] The invention also includes humanized antibodies 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).

[0190] The invention further contemplates antibodies 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.

[0191] The invention also contemplates fragments of the antibody 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: 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.

[0192] 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: 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.

[0193] 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: 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.

[0194] The invention also contemplates antibody fragments 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.

[0195] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody 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.

[0196] 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 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.

[0197] In one embodiment of the invention described herein (*infra*), Fab fragments 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*.

Antibody Ab6

[0198] In one embodiment, the invention includes humanized antibodies 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).

[0199] The invention also includes humanized antibodies 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).

[0200] The invention further includes humanized antibodies 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).

[0201] The invention also includes humanized antibodies 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).

[0202] The invention further contemplates antibodies 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.

[0203] The invention also contemplates fragments of the antibody 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: 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.

[0204] 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: 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.

[0205] 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: 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.

[0206] The invention also contemplates antibody fragments 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: 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.

[0207] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody 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.

[0208] 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 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.

[0209] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6. In another embodiment of the invention, anti-CGRP antibodies 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

[0210] In one embodiment, the invention includes chimeric antibodies 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).

[0211] The invention also includes chimeric antibodies 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).

[0212] The invention further includes chimeric antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:

QEQLKESGGRLVTPGTSLTLTCTVSGIDLSNHYMQWVRQAPGKGLEWIGVVGING RTYYASWAKGRFTISRTSSTTVDLKMTRLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 63).

[0213] The invention also includes chimeric antibodies 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).

[0214] The invention further contemplates antibodies 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.

[0215] The invention also contemplates fragments of the antibody 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: 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.

[0216] 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: 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.

[0217] 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: 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.

[0218] The invention also contemplates antibody fragments 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.

[0219] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody 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.

[0220] 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 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.

[0221] In one embodiment of the invention described herein (*infra*), Fab fragments 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

[0222] In one embodiment, the invention includes humanized antibodies 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).

[0223] The invention also includes humanized antibodies 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).

[0224] The invention further includes humanized antibodies 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).

[0225] The invention also includes humanized antibodies 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).

[0226] The invention further contemplates antibodies 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.

[0227] The invention also contemplates fragments of the antibody 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: 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.

[0228] 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: 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.

[0229] 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: 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.

[0230] The invention also contemplates antibody fragments 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: 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.

[0231] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody 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.

[0232] 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 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.

[0233] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab8. In another embodiment of the invention, anti-CGRP antibodies 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

[0234] In one embodiment, the invention includes chimeric antibodies 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).

[0235] The invention also includes chimeric antibodies 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).

[0236] The invention further includes chimeric antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:

QSLEESGGRLVTPGTPLTLTCTVSGIGLSSYYMQWVRQSPGRGLEWIGVIGSDGKT YYATWAKGRFTISKTSSTTVDLRMASLTTEDTATYFCTRGDIWGPGTLVTVSS (SEQ ID NO: 83).

[0237] The invention also includes chimeric antibodies 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).

[0238] The invention further contemplates antibodies 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 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.

[0239] The invention also contemplates fragments of the antibody 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: 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.

[0240] 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: 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.

[0241] 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: 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.

[0242] The invention also contemplates antibody fragments 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: 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.

[0243] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody 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.

[0244] 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 Ab9, the Fab fragment 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.

[0245] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab9. In another embodiment of the invention, anti-CGRP antibodies 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

[0246] In one embodiment, the invention includes humanized antibodies 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).

[0247] The invention also includes humanized antibodies 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).

[0248] The invention further includes humanized antibodies 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).

[0249] The invention also includes humanized antibodies 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).

[0250] The invention further contemplates antibodies 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.

[0251] The invention also contemplates fragments of the antibody 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: 91 or SEQ ID NO: 92. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 93 or SEQ ID NO: 94.

[0252] 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: 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.

[0253] 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: 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.

[0254] The invention also contemplates antibody fragments 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.

[0255] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody 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.

[0256] 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 Ab10, the Fab fragment 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.

[0257] In one embodiment of the invention described herein (*infra*), Fab fragments 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

[0258] In one embodiment, the invention includes chimeric antibodies 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).

[0259] 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).

[0260] The invention further includes chimeric antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:

QSLEESGGRLVTPGGSLTLTCTVSGIDVTNYYMQWVRQAPGKGLEWIGVIGVNGK RYYASWAKGRFTISKTSSTTVDLKMTSLTTEDTATYFCARGDIWGPGTLVTVSS (SEQ ID NO: 103).

[0261] The invention also includes chimeric antibodies 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).

[0262] The invention further contemplates antibodies 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.

[0263] The invention also contemplates fragments of the antibody 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: 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.

[0264] 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: 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.

[0265] 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: 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.

[0266] The invention also contemplates antibody fragments 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: 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.

[0267] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody 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.

[0268] 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 Ab11, the Fab fragment 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.

[0269] In one embodiment of the invention described herein (*infra*), Fab fragments 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

[0270] In one embodiment, the invention includes humanized antibodies 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).

[0271] The invention also includes humanized antibodies 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).

[0272] 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).

[0273] The invention also includes humanized antibodies 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).

[0274] The invention further contemplates antibodies 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 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.

[0275] The invention also contemplates fragments of the antibody 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: 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.

[0276] 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: 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.

[0277] 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: 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.

[0278] The invention also contemplates antibody fragments 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: 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.

[0279] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody 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.

[0280] 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 Ab12, the Fab fragment 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.

[0281] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab12. In another embodiment of the invention, anti-CGRP antibodies 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

[0282] In one embodiment, the invention includes chimeric antibodies 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).

[0283] The invention also includes chimeric antibodies 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).

[0284] The invention further includes chimeric antibodies 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).

[0285] The invention also includes chimeric antibodies 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).

[0286] The invention further contemplates antibodies 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.

[0287] The invention also contemplates fragments of the antibody 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.

[0288] 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: 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.

[0289] 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: 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.

[0290] The invention also contemplates antibody fragments 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.

[0291] In a particularly preferred embodiment of the invention, the chimeric anti-CGRP antibody 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.

[0292] 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 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.

[0293] In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab13. In another embodiment of the invention, anti-CGRP antibodies 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

[0294] In one embodiment, the invention includes humanized antibodies 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).

[0295] The invention also includes humanized antibodies 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).

[0296] The invention further includes humanized antibodies 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).

[0297] The invention also includes humanized antibodies 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).

[0298] The invention further contemplates antibodies 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.

[0299] The invention also contemplates fragments of the antibody 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: 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.

[0300] 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: 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.

[0301] 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: 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.

[0302] The invention also contemplates antibody fragments 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.

[0303] In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody 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.

[0304] 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 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.

[0305] In one embodiment of the invention described herein (*infra*), Fab fragments 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*.

[0306] 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 further comprises the kappa constant light chain sequence comprising the sequence set forth below:

[0307] VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 283).

[0308] In another preferred embodiment, the anti-CGRP antibodies described herein further comprises the gamma-1 constant heavy chain polypeptide sequence comprising the sequence set forth below:

[0309] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV

DGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK (SEQ ID NO: 284).

[0310] In another embodiment, the invention contemplates an isolated anti-CGRP antibody comprising 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; 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, wherein one or more of the framework residues (FR 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. The invention contemplates humanized and chimeric forms of these antibodies. 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.

[0311] In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

[0312] In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof 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 inhibit the association of CGRP with CGRP-R and/or additional proteins and/or multimers thereof, and/or antagonizes the biological effects thereof.

[0313] As stated in paragraph [0127] herein, antibodies and fragments thereof 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.

[0314] 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 derivatization 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.

[0315] 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.

[0316] 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.

[0317] 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).

[0318] Alternatively, antibodies or fragments thereof 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.

[0319] 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 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^{3}H) and Phosphorus 32 (^{32}P).

[0320] 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.

[0321] 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)).

[0322] 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 (^{32}P), Scandium-47 (^{47}Sc), Copper-67 (^{67}Cu), Gallium-67 (^{67}Ga), Yttrium-88 (^{88}Y), Yttrium-90 (^{90}Y), Iodine-125 (^{125}I), Iodine-131 (^{131}I), Samarium-153 (^{153}Sm), Lutetium-177 (^{177}Lu), Rhenium-186 (^{186}Re) or Rhenium-188 (^{188}Re), and alpha-emitters such as Astatine-211 (^{211}At), Lead-212 (^{212}Pb), Bismuth-212 (^{212}Bi) or -213 (^{213}Bi) or Actinium-225 (^{225}Ac).

[0323] 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).

[0324] 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.

[0325] 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.

[0326] 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*.

[0327] 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.

[0328] 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

[0329] In another embodiment, the invention contemplates one or more anti-human CGRP antibodies or antibody fragments thereof which specifically bind to the same ovelappping linear or conformational epitope(s) and/or competes for binding to the same ovelappping 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 ovelappping linear or conformational epitope(s) and/or competes for binding to the same ovelappping linear or conformational epitope(s) on an intact human CGRP polypeptide or a fragment thereof as Ab3, Ab6, Ab13, or Ab14.

[0330] 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. In a particularly preferred embodiment of the invention, the chimeric or humanized anti-CGRP antibodies are selected from Ab3, Ab6, Ab13, or Ab14.

[0331] In a further embodiment of the invention is contemplated a method of reducing, treating or preventing diseases or disorders associated with CGRP by affecting those biological activities mediated *via* CGRP, thereby avoiding the biological activities mediated via binding of CGRP to CGRP-R. In one embodiment, the disease or disorder associated with CGRP is migraine or another disorder wherein CGRP elicits pain, headache, pain, cancer, overactive bladder, or weightloss. A further non-limiting listing of diseases and disorders associated with CGRP is provided herein.

[0332] Another preferred embodiment of the invention contemplates the use of Fab polypeptide sequences for the treatment of migraines and headaches in a patient. Non-limiting types of migraines and headaches that may be treated using Fab polypeptide sequences are provided elsewhere in this disclosure.

[0333] In another embodiment of the invention, the anti-human CGRP antibody is an antibody which specifically binds to the same ovelappping 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.

[0334] The invention is also directed to an anti-CGRP antibody 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.

[0335] In another embodiment, the invention is also directed to an isolated anti-CGRP antibody or antibody fragment comprising one or more of the CDRs contained in the V_H 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 V_L polypeptide sequences selected from: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, or 131, or a variant thereof.

[0336] 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.

[0337] 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.

[0338] The invention further contemplates that the one or more anti-human CGRP antibodies discussed above are aglycosylated; 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.

[0339] The invention further contemplates one or more anti-human CGRP antibodies 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.

[0340] In one embodiment of the invention, the anti-human CGRP antibody or fragment 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.

[0341] In another embodiment, the disease 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.

[0342] In another embodiment of the invention, the disease 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.

[0343] The invention further contemplates anti-human CGRP antibodies or fragments directly or indirectly attached to a detectable label or therapeutic agent.

[0344] 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.

[0345] The invention also contemplates a method of treatment comprising administering to a patient with a disease or condition associated with CGRP expressing cells 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.

[0346] In a non-limiting embodiment of the invention, another therapeutic agent or regimen includes 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.

[0347] 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.

[0348] The anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, 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 (K_D) 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.

[0349] 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}.

[0350] 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. Non-limiting examples of diseases and disorders associated with CGRP are set forth herein.

Polynucleotides Encoding Anti-CGRP Antibody Polypeptides

Antibody Ab1

[0351] 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:

[0352] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACC TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT ACATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGG GACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTA CTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGG AGGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 141).

[0353] 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:

[0354] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACC TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT ACATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGG GACACAGTTCACTCTCACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTA CTACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGG AGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCT TCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGC TGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACA GCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAA ACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 142).

[0355] 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:

[0356] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC CCTGACACTCACCTGCACAGTCTCTGGACTCGACCTCAGTAGCTACTACATGCA

ATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTA
TTAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC
AGAGCCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACCCTCG
TCACCGTCTCGAGC (SEQ ID NO: 143).

[0357] 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:

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGAC
ACTCACCTGCACAGTCTCTGGACTCGACCTCAGTAGCTACTACATGCAATGGGT
CCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTATTAATG
ATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGAGCC
TCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGC
CACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACCCTCGTCACCG
TCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA
AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC
CCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA
CACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATC
ACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA
CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGT
CAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCC
CTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG
GGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGA
GTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG

CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 144).

[0358] 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.

[0359] 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.

[0360] 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.

[0361] 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.

[0362] 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

[0363] 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:

[0364] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACCT

AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA
CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT
ACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 151).

[0365] 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:

[0366] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACCT
AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA
CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT
ACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 152).

[0367] 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:

[0368] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG
GTCCCTGAGACTCTCCTGTGCAGTCTCTGGACTCGACCTCAGTAGCTACTACAT
GCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTG
GTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATC
TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC

TGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 153).

[0369] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGTCTCTGGACTCGACCTCAGTAGCTACTACATGCAATG
GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTATCA
ATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGA
GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT

CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 154).

[0370] 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.

[0371] 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.

[0372] 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.

[0373] 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.

[0374] 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

[0375] 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:

[0376] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACCT
AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA

CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT
ACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 161).

[0377] 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:

[0378] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATGATAACAACTACCT
AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA
CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT
ACTGTCTAGGCAGTTATGATTGTAGTAGTGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 162).

[0379] 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:

[0380] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG
GTCCCTGAGACTCTCCTGTGCAGTCTCTGGACTCGACCTCAGTAGCTACTACAT
GCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTG
GTATCAATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATC
TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC
TGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 163).

[0381] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGTCTCTGGACTCGACCTCAGTAGCTACTACATGCAATG
GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTATCA
ATGATAACACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGA
GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCCAAATCT
TGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGT
CCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
AAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCC
CGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 164).

[0382] 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.

[0383] 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.

[0384] 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.

[0385] 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.

[0386] 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

[0387] 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:

[0388] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAACAACTGATCTATGATG CATCCACTCTGGCGTCTGGGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGGCGTGCAGTGTAACGATGCTGCCGCTTAC TACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 171).

[0389] 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:

[0390] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAACAACTGATCTATGATG CATCCACTCTGGCGTCTGGGGTCCCATCGCGGTTCAGCGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGGCGTGCAGTGTAACGATGCTGCCGCTTAC TACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 172).

[0391] 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:

[0392] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC CCTGACACTCACCTGTTCCGTCTCTGGCATCGACCTCAGTGGCTACTACATGAA CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTA TTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC AAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA CACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCGGGCACCCTCG TCACCGTCTCGAGC (SEQ ID NO: 173).

[0393] 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:

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGAC
ACTCACCTGTTCCGTCTCTGGCATCGACCTCAGTGGCTACTACATGAACTGGGT
CCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTATTAATG
GTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACC
TCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGC
CACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCGGGCACCCTCGTCACCG
TCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA
AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC
CCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA
CACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATC
ACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA
CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGT
CAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCC
CTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG
GGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGA
GTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG
CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGC
AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA
CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID
NO: 174).

[0394] 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.

[0395] 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.

[0396] 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.

[0397] 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.

[0398] 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

[0399] 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:

[0400] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATG CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT ACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAG GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 181).

[0401] 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:

[0402] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATG CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT ACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAG GAACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 182).

[0403] 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:

[0404] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGTGGCTACTACAT GAACTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTG GTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATC TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC TGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 183).

[0405] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGTGGCTACTACATGAACTG GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTATTA ATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGA

GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 184).

[0406] 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.

[0407] 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.

[0408] 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.

[0409] 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.

[0410] 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*.

Antibody Ab6

[0411] 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:

[0412] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATG CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT ACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAG GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 191).

[0413] 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:

[0414] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATCATAACACCTACCT GGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATGATG CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT

ACTGTCTGGGCAGTTATGATTGTACTAATGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 192).

[0415] 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:

[0416] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG
GTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGTGGCTACTACAT
GAACTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTG
GTATTAATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATC
TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC
TGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 193).

[0417] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGTGGCTACTACATGAACTG
GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTATTA
ATGGTGCCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGA
GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG

CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCCAAATCT
TGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGT
CCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
AAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCC
CGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 194).

[0418] 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.

[0419] 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.

[0420] 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.

[0421] 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.

[0422] 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

[0423] 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:

[0424] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATAATTACAACTACCT TGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC TACTGTCTAGGCAGTTATGACTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 201).

[0425] 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:

[0426] CAAGTGCTGACCCAGACTGCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTATAATTACAACTACCT TGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCTCATCGCGATTCAAAGGCAGTGGATCTGGG ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC TACTGTCTAGGCAGTTATGACTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGA GGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT

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

[0427] 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:

[0428] CAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGA
CATCCCTGACACTCACCTGCACCGTCTCTGGAATCGACCTCAGTAACCACTACA
TGCAATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCGTT
GGTATTAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCAT
CTCCAGAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGGCTGACAACCG
AGGACACGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACC
CTGGTCACCGTCTCGAGC (SEQ ID NO: 203).

[0429] 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:

CAGGAGCAGCTGAAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACATCCCT
GACACTCACCTGCACCGTCTCTGGAATCGACCTCAGTAACCACTACATGCAAT
GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCGTTGGTATT
AATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAG
AACCTCGTCGACCACGGTGGATCTGAAAATGACCAGGCTGACAACCGAGGACA
CGGCCACCTATTTCTGTGCCAGAGGGGACATCTGGGGCCCAGGCACCCTGGTC
ACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCC
TCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTA
CTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCG
TGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCG
TGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG
AATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTT
GTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGA

CCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGG
ACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGC
CGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA
AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCC
GAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAA
CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCC
GTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAG
AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCT
GCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 204).

[0430] 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.

[0431] 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.

[0432] 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.

[0433] 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.

[0434] 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

[0435] 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:

[0436] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTACAATTACAACTACCTT GCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTAC ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGAC AGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTA CTGTCTGGGCAGTTATGATTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGAGG AACCAAGGTGGAAATCAAACGT (SEQ ID NO: 211).

[0437] 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:

[0438] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAGTGTTTACAATTACAACTACCTT GCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTAC ATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGAC AGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTA CTGTCTGGGCAGTTATGATTGTAGTACTGGTGATTGTTTTGTTTTCGGCGGAGG AACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCC GCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAA TAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCC AATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCAC CTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACAC AAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAA GAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 212).

[0439] 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:

[0440] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG
GTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGTAACCACTACAT
GCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCGTTG
GTATCAATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATC
TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC
TGAGGACACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 213).

[0441] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGTCTCTGGAATCGACCTCAGTAACCACTACATGCAATG
GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCGTTGGTATCA
ATGGTCGCACATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGA
GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTGCTAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG

TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 214).

[0442] 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.

[0443] 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.

[0444] 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.

[0445] 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.

[0446] 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

[0447] 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:

[0448] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTATAATAACAACTACC TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT ACGTCCACTCTGGCATCTGGGGTCTCATCGCGATTCAGAGGCAGTGGATCTGG GACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTT ACTACTGTCTAGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCG GAGGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 221).

[0449] 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:

[0450] CAAGTGCTGACCCAGACTCCATCCCCCGTGTCTGCAGCTGTGGGAAG CACAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTATAATAACAACTACC TAGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCT ACGTCCACTCTGGCATCTGGGGTCTCATCGCGATTCAGAGGCAGTGGATCTGG GACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTT ACTACTGTCTAGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCG GAGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATC TTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTG CTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGC CCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGAC AGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGA AACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC ACAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 222).

[0451] 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:

[0452] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACC CCTGACACTCACCTGCACAGTCTCTGGAATCGGCCTCAGTAGCTACTACATGCA

GTGGGTCCGCCAGTCTCCAGGGAGGGGGCTGGAATGGATCGGAGTCATTGGTA
GTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCC
AAGACCTCGTCGACCACGGTGGATCTGAGAATGGCCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTACCAGAGGGGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGC (SEQ ID NO: 223).

[0453] 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:

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGAC
ACTCACCTGCACAGTCTCTGGAATCGGCCTCAGTAGCTACTACATGCAGTGGGT
CCGCCAGTCTCCAGGGAGGGGGCTGGAATGGATCGGAGTCATTGGTAGTGATG
GTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAAGACC
TCGTCGACCACGGTGGATCTGAGAATGGCCAGTCTGACAACCGAGGACACGGC
CACCTATTTCTGTACCAGAGGGGACATCTGGGGCCCGGGGACCCTCGTCACCG
TCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA
AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC
CCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA
CACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATC
ACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA
CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGT
CAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCC
CTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG
GGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGA
GTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG

CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 224).

[0454] 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.

[0455] 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.

[0456] 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.

[0457] 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.

[0458] 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

[0459] 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:

[0460] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTACAATAACAACTACCT

AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA
CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT
ACTGTCTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 231).

[0461] 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:

[0462] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTACAATAACAACTACCT
AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA
CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT
ACTGTCTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 232).

[0463] 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:

[0464] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG
GTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGGCCTCAGTAGCTACTACAT
GCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTG
GTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATC
TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC

TGAGGACACTGCTGTGTATTTCTGTACCAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 233).

[0465] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGTCTCTGGAATCGGCCTCAGTAGCTACTACATGCAATG
GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTAGTG
ATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAGA
GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTACCAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT

CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 234).

[0466] 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.

[0467] 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.

[0468] 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.

[0469] 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.

[0470] 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

[0471] 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:

[0472] CAGGTGCTGACCCAGACTGCATCCCCCGTGTCTCCAGCTGTGGGAAG
CACAGTCACCATCAATTGCCGGGCCAGTCAGAGTGTTTATTATAACAACTACCT
AGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGG

ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC
TACTGTCTAGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGA
GGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 241).

[0473] 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:

[0474] CAGGTGCTGACCCAGACTGCATCCCCCGTGTCTCCAGCTGTGGGAAG
CACAGTCACCATCAATTGCCGGGCCAGTCAGAGTGTTTATTATAACAACTACCT
AGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCTCATCGCGGTTCAAAGGCAGTGGATCTGGG
ACACAGTTCACTCTCACCATCAGCGACGTGCAGTGTGACGATGCTGCCACTTAC
TACTGTCTAGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGA
GGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 242).

[0475] 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:

[0476] CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGAGGATC
CCTGACACTCACCTGCACAGTCTCTGGAATCGACGTCACTAACTACTATATGCA
ATGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTG
TGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCC
AAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGA
CACGGCCACCTATTTCTGTGCCAGAGGCGACATCTGGGGCCCGGGGACCCTCG
TCACCGTCTCGAGC (SEQ ID NO: 243).

[0477] 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:

CAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGAGGATCCCTGAC
ACTCACCTGCACAGTCTCTGGAATCGACGTCACTAACTACTATATGCAATGGGT
CCGCCAGGCTCCAGGGAAGGGGCTGGAATGGATCGGAGTCATTGGTGTGAATG
GTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAAAACC
TCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACAACCGAGGACACGGC
CACCTATTTCTGTGCCAGAGGCGACATCTGGGGCCCGGGGACCCTCGTCACCG
TCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCA
AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC
CCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA
CACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATC
ACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA
CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGT
CAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCC
CTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG
GGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG
AACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGA
GTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG
CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGC
AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA
CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA (SEQ ID NO: 244).

[0478] 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.

[0479] 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.

[0480] 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.

[0481] 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.

[0482] 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

[0483] 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:

[0484] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCGGGCCAGTCAGAGTGTTTACTATAACAACTACCT AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT ACTGTCTGGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGAG GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 251).

[0485] 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:

[0486] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCAATTGCCGGGCCAGTCAGAGTGTTTACTATAACAACTACCT
AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA
CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA
CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT
ACTGTCTGGGCAGTTATGATTGTAGTAATGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 252).

[0487] 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:

[0488] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG
GTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGACGTCACTAACTACTACAT
GCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTG
GTGTGAATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATC
TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC
TGAGGACACTGCTGTGTATTTCTGTGCCAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 253).

[0489] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGTCTCTGGAATCGACGTCACTAACTACTACATGCAATG
GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTGTGA
ATGGTAAGAGATACTACGCGAGCTGGGCGAAAGGCCGATTCACCATCTCCAGA
GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTGCCAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG
CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGG
GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCC
GGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG
GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCG
TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 254).

[0490] 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.

[0491] 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.

[0492] 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.

[0493] 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.

[0494] 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

[0495] 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:

[0496] GCCATCGTGATGACCCAGACTCCATCTTCCAAGTCTGTCCCTGTGGGA GACACAGTCACCATCAATTGCCAGGCCAGTGAGAGTCTTTATAATAACAACGC CTTGGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATG ATGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAGTGGCGGTGGGTCT GGGACACAGTTCACTCTCACCATCAGTGGCGTGCAGTGTGACGATGCTGCCAC TTACTACTGTGGAGGCTACAGAAGTGATAGTGTTGATGGTGTTGCTTTCGCCGG AGGGACCGAGGTGGTGGTCAAACGT (SEQ ID NO: 261).

[0497] 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:

[0498] GCCATCGTGATGACCCAGACTCCATCTTCCAAGTCTGTCCCTGTGGGA GACACAGTCACCATCAATTGCCAGGCCAGTGAGAGTCTTTATAATAACAACGC CTTGGCCTGGTTTCAGCAGAAACCAGGGCAGCCTCCCAAGCGCCTGATCTATG ATGCATCCAAACTGGCATCTGGGGTCCCATCGCGGTTCAGTGGCGGTGGGTCT GGGACACAGTTCACTCTCACCATCAGTGGCGTGCAGTGTGACGATGCTGCCAC TTACTACTGTGGAGGCTACAGAAGTGATAGTGTTGATGGTGTTGCTTTCGCCGG AGGGACCGAGGTGGTGGTCAAACGTACGGTGGCTGCACCATCTGTCTTCATCT TCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGC TGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACA GCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAA ACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA CAAAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 262).

[0499] 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:

[0500] CAGTCGGTGGAGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGAT CCCTGACACTCACCTGCACAGCCTCTGGATTCGACTTCAGTAGCAATGCAATGT GGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATGCATTTAC AATGGTGATGGCAGCACATACTACGCGAGCTGGGTGAATGGCCGATTCTCCAT CTCCAAAACCTCGTCGACCACGGTGACTCTGCAACTGAATAGTCTGACAGTCG CGGACACGGCCACGTATTATTGTGCGAGAGATCTTGACTTGTGGGGCCCGGGC ACCCTCGTCACCGTCTCGAGC (SEQ ID NO: 263).

[0501] 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:

CAGTCGGTGGAGGAGTCCGGGGGAGGCCTGGTCCAGCCTGAGGGATCCCTGAC ACTCACCTGCACAGCCTCTGGATTCGACTTCAGTAGCAATGCAATGTGGTGGGT CCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGATGCATTTACAATGGTG ATGGCAGCACATACTACGCGAGCTGGGTGAATGGCCGATTCTCCATCTCCAAA

ACCTCGTCGACCACGGTGACTCTGCAACTGAATAGTCTGACAGTCGCGGACAC
GGCCACGTATTATTGTGCGAGAGATCTTGACTTGTGGGGCCCGGGCACCCTCGT
CACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTC
CTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT
ACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGC
GTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGC
GTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGT
GAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCT
TGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGT
CCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
AAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCC
CGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 264).

[0502] 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.

[0503] 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.

[0504] 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.

[0505] 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.

[0506] 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

[0507] 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:

[0508] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTACAATAACAACTACCT AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT ACTGTCTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAG GAACCAAGGTGGAAATCAAACGT (SEQ ID NO: 271).

[0509] 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:

[0510] CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCAATTGCCAGGCCAGTCAGAATGTTTACAATAACAACTACCT AGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCAACTGATCTATTCTA CATCCACTCTGGCATCTGGGGTCCCATCTCGTTTCAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATT

ACTGTCTGGGCAGTTATGATTGTAGTCGTGGTGATTGTTTTGTTTTCGGCGGAG
GAACCAAGGTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTC
CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG
AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGC
ACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGTTAG (SEQ ID NO: 272).

[0511] 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:

[0512] GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGG
GTCCCTGAGACTCTCCTGTGCAGTCTCTGGAATCGGCCTCAGTAGCTACTACAT
GCAATGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTG
GTAGTGATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATC
TCCAGAGACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGC
TGAGGACACTGCTGTGTATTTCTGTACCAGAGGGGACATCTGGGGCCAAGGGA
CCCTCGTCACCGTCTCGAGC (SEQ ID NO: 273).

[0513] 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:

GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGTCTCTGGAATCGGCCTCAGTAGCTACTACATGCAATG
GGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGGAGTCATTGGTAGTG
ATGGTAAGACATACTACGCGACCTGGGCGAAAGGCCGATTCACCATCTCCAGA
GACAATTCCAAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAGCTGAGGA
CACTGCTGTGTATTTCTGTACCAGAGGGGACATCTGGGGCCAAGGGACCCTCG
TCACCGTCTCGAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCT
CCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGG

CGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAG
CGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCCAAATCT
TGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCG
GACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGT
CCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
AAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCC
CGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC
CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA
(SEQ ID NO: 274).

[0514] 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.

[0515] 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.

[0516] 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.

[0517] 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.

[0518] 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*.

[0519] In one embodiment, the invention is directed to an isolated polynucleotide comprising a polynucleotide encoding an anti-CGRP V_H 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 V_H polypeptide or a conservative amino acid substitution.

[0520] In another embodiment, the invention is directed to an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-CGRP V_L 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 V_L polypeptide or a conservative amino acid substitution.

[0521] 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.

[0522] 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 V_L or V_H 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.

[0523] Host cells and vectors comprising said polynucleotides are also contemplated.

[0524] 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

[0525] 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

[0526] 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

[0527] In another embodiment, the present invention contemplates methods for producing anti-CGRP antibodies and fragments thereof. 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.

[0528] 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).

[0529] 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).

[0530] Antibody polypeptides of the invention having CGRP binding specificity 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.

[0531] 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.

[0532] 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.

[0533] 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.

[0534] 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.

[0535] 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.

[0536] 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.

[0537] 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

[0538] The invention also includes screening assays designed to assist in the identification of diseases and disorders associated with CGRP in patients exhibiting symptoms of a CGRP associated disease or disorder.

[0539] 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. The presence of CGRP, or elevated levels thereof 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.

[0540] 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.

[0541] 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.

[0542] 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.

[0543] 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.

[0544] 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).

[0545] 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.

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

[0546] 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, diseases and disorders associated with CGRP. 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.

[0547] 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, 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.

[0548] 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, the following non-limiting listing of 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.

[0549] 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.

[0550] 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.

[0551] 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: overactive bladder and other urinary conditions, gastro-esophageal reflux 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, pruritis, or pancreatitis. Also, the subject CGRP antibodies and antibody fragments may be used alone or in conjunction with other active agents, e.g., opioids and non-opioid analgesics such as

NSAIDs to elicit analgesia or to potentiate the efficacy of another analgesic or to prevent or alleviate tolerance to a specific analgesic such as morphine or related opioid analgesics. Evidence for role of CGRP in blocking / reversing development of morphine – induced analgesia: is the fact that CGRP8-37 and CGRP Receptor antagonist (BIBN4096BS) reportedly prevent / reverse development of morphine tolerance -(Powell et al., 2000 J Brit J Pharmacol (131):875; Menard et al., 1996 J Neurosci (16):2342; Wang et al., 2009 FASEB J (23):2576; Wang et al., 2010 Pain (151):194)

[0552] The subject antibodies potentially may be combined with any opioid analgesic or NSAID or other analgesic, potentially another antibody, in order to increase or enhance pain management, or to reverse or suppress tolerance to an analgesic such as an opioid analgesic compound. This may allow for such analgesic compounds to be administered for longer duration or at reduced dosages thereby potentially alleviating adverse side effects associated therewith.

[0553] The term "opioid analgesic" herein refers to all drugs, natural or synthetic, with morphine-like actions. The synthetic and semi-synthetic opioid analgesics are derivatives of five chemical classes of compound: phenanthrenes; phenylheptylamines; phenylpiperidines; morphinans; and benzomorphans, all of which are within the scope of the term. Exemplary opioid analgesics include codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine or pharmaceutically acceptable salts thereof.

[0554] The term "NSAID" refers to a non-steroidal anti-inflammatory compound. NSAIDs are categorized by virtue of their ability to inhibit cyclooxygenase. Cyclooxygenase 1 and cyclooxygenase 2 are two major isoforms of cyclooxygenase and most standard NSAIDs are mixed inhibitors of the two isoforms. Most standard NSAIDs fall within one of the following five structural categories: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and slindac; (3) fenamic acid derivatives, such as mefenamic acid and meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, sudoxicam, and isoxicam. Another class of

NSAID has been described which selectively inhibit cyclooxygenase 2. Cox-2 inhibitors have been described, e.g., in U.S. Pat. Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain exemplary COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), rofecoxib, MK-966, nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof.

[0555] In some embodiments, aspirin and/or acetaminophen may be taken in conjunction with the subject CGRP antibody or fragment. Aspirin is another type of non-steroidal anti-inflammatory compound.

[0556] Exemplary, non-limiting diseases and disorders that can be treated and/or prevented by the administration of the CGRP antibodies of the present invention include, pain resulting from any condition associated with neurogenic, neuropathic, inflammatory, thermal or nociceptic pain. Preferably the disorder will be associated with increased CGRP at the pain site. In certain embodiments of neuropathic pain, referred trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, reflex sympathetic dystrophy and neurogenic pain conditions are preferably treated. In other embodiments, cancer pain, particularly, bone cancer pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, post-operative incision pain, fracture pain, osteoporotic fracture pain, osteoporosis, gout joint pain, diabetic neuropathy, sciatica, pains associated with sickle cell crises, migraine, and other neuropathic and/or nociceptic pain are preferably treated. Thus, the present invention includes methods of treating, preventing, and/or ameliorating any disease or disorder associated with CGRP activity or CGRP upregulation (including any of the above mentioned exemplary diseases, disorders and conditions) through use of the antibodies and antibody fragments of the invention. The therapeutic methods of the present invention comprise administering to a subject any formulation comprising an anti-CGRP antibody as disclosed herein alone or in association with another active agent.

[0557] . The subject to which the pharmaceutical formulation is administered can be, e.g., any human or non-human animal that is in need of such treatment, prevention and/or

amelioration, or who would otherwise benefit from the inhibition or attenuation of CGRP-mediated activity. For example, the subject can be an individual that is diagnosed with, or who is deemed to be at risk of being afflicted by any of the aforementioned diseases or disorders. The present invention further includes the use of any of the pharmaceutical formulations disclosed herein in the manufacture of a medicament for the treatment, prevention and/or amelioration of any disease or disorder associated with CGRP activity (including any of the above mentioned exemplary diseases, disorders and conditions).

Administration

[0558] 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.

[0559] 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.

[0560] 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 [0552] and [0553].

[0561] 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.

[0562] 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.

[0563] 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.

[0564] 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.

[0565] 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.

[0566] 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.

[0567] 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.

[0568] 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.

[0569] 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.

[0570] 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.

[0571] 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.

[0572] 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.

[0573] 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.

[0574] 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.

[0575] 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.

[0576] 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.

[0577] 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.

[0578] 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.

[0579] 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.

[0580] 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.

[0581] 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*

[0582] By using the antibody selection protocol described herein, one can generate an extensive panel of antibodies.

Immunization Strategy

[0583] Rabbits were immunized with human CGRPα (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

[0584] To identify and characterize antibodies that bind to human CGRPα, antibody-containing solutions were tested by ELISA. Briefly, neutravidin coated plates (Thermo Scientific), were coated with N-term biotinylated human CGRPα (50μL per well, 1μg/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-HARP (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)

[0585] 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 CGRPα 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 CGRPα 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

[0586] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[0587] 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.

[0588] 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

[0589] 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

[0590] Cells were pre-mixed with the biotinylated human CGRPα as follows. Cells were washed again and resuspended at 1E07 cells/80 μL medium. Biotinylated human CGRPα 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:

[0591] 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 μl 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.

[0592] 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.

[0593] 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% CO_2.

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

[0594] 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 (50µL 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

[0595] 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

[0596] 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.

[0597] 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.

[0598] 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

[0599] 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

[0600] 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

[0601] 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.

[0602] 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

[0603] 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.

[0604] 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).

[0605] 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*

[0606] 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.

[0607] 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

[0608] 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*

[0609] 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.

[0610] 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.

[0611] 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.

[0612] 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*

[0613] 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*

[0614] 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 ^{125}I radiolabeld human CGRPα (0.03nM)

for 30 minutes at room temperature. Non-specific binding was estimated in the presence of 0.1μM human CGRPα. Membranes were filtered and washed. The filters were then counted to determine ^{125}I radiolabeld human CGRPα specifically bound.

[0615] 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*

[0616] 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)).

[0617] 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 O-rings (~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.

[0618] 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.

[0619] Results: Figures 39 and 40 demonstrates that anti-CGRP antibodies Ab3 and Ab6 reduced vasodilation in this model following capsaicin administration.

Example 8 Effect of CGRP Antibody Administration on Overactive Bladder

[0620] Experiments were conducted to assess the potential efficacy of an anti-CGRP antibody administration on bladder continence and overactive bladder. Bladder continence is a balance between urethral closure and detrusor muscle activity, and overactive bladder is a condition characterized by urgency, urinary incontinence, frequency and nocturia. Some anecdotal evidence reported in the literature suggests that CGRP may be involved with bladder continence and may correlate to and perhaps play a causal role in overactive bladder disease pathology. Accordingly, it was hoped that the inventive anti-CGRP antibodies, especially given their high affinity to CGRP, would potentially help prevent or alleviate this sometimes debilitating condition. (The evidence that that CGRP may play a role in overactive bladder includes the fact that CGRP is present in the urinary tract, DRG and spinal cord (Wharton et al., 1986 Neurosci (3):727) Also, C-fiber afferents are critical for carrying impulses involved in micturition to spinal cord (Yoshida et al., 2011 J Pharmacol Sci (112):128) and these fibers are affected by CGRP. Further, it has been reported that intravesical administration of Botox suppresses CGRP and significantly reduces intercontraction interval in an acetic acid induced bladder pain model (Chuang et al., 2004 J Urol (172):1529; Chuang et al., 2009 J Urol (182):786)). Moreover, it has been recently reported that the administration of an anti-CGRP antibody purportedly reduces the number of bladder contractions in turpentine-oil – induced overactive bladder model (Pfizer PCT Patent Application WO 2011/024113)).

[0621] **Materials and Methods**

[0622] Animals:

[0623] Female Sprague-Dawley rats (247 – 299 g) (Charles River Laboratories, Saint Germain sur l'Arbresle, France) were delivered to the laboratory at least 5 days before the experiments in order to be acclimatized to laboratory conditions. They were housed 3 per cage (polypropylene type E cages size: 1032 cm^2) and given food (Teklad 2016 global rodents, Harlan, 03800 Gannat, France) and water *ad libitum*. Sawdust (Souralit 2912 plus, Souralit, 17080 Girona, Spain) bedding for rodent cages was changed twice weekly. The animal room temperature (20 ± 2 °C) was maintained with a 12/12 hour alternating light-dark cycle (light phase 7 am: 7 pm) and relative humidity maintained at 40-70%.

[0624] Laboratory equipment

[0625] Bladder catheters were connected *via* a T-tube to a strain gauge MX 860 Novatrans III Gold (Medex Medical SARL, Nantes-Carquefou, France) and a syringe pump (70-2208 Model II plus, Harvard Apparatus, Les Ullis, France and Razel R-99E, Fisher Bioblock, Illkirch, France). Intravesical pressure was recorded continuously using a PowerLab interface (ADInstruments Pty Ltd, Castle-Hill, Australia) and Chart® software running on a PC. Data were analyzed with Microsoft Excel ® software.

[0626] Test substances

[0627] Test Anti-CGRP antibody (Ab3)

[0628] Negative control antibody (Anti-digitoxin antibody).

[0629] Chemical reagents

[0630] Physiological saline (NaCl 0.9%) (batch n° 11043411, CAS n° 7647-14- 5) was purchased from B-Braun *via* Centravet (Lapalisse, France).

[0631] Anesthetic substances

[0632] Urethane (batch n° BCBC9294, CAS n° 51-79-6) and sodium pentobarbital (batch n° 150A1, CAS n°76- 74-4) were supplied by Sigma-Aldrich (St Quentin Fallavier, France) and Centravet (Lapalisse, France), respectively.

[0633] **Experimental groups**

[0634] Two experimental groups of 10 rats were used in the experiments. Each group was administered 10 mg/kg of either the control or the anti-CGRP antibody:

[0635] **Study design**

[0636] Experimental procedure

[0637] Female rats were administered test antibody or negative control antibody intravenously at a dose of 10 mg/kg, 18 hours prior to experiments using a tail vein injection. Fifteen (15) hours later, rats were anesthetized with urethane (1.2 g/kg, subcutaneous (s.c.). Three (3) hours after the s.c. administration of urethane, a polyethylene catheter (0.58 and 0.96 mm of internal and outer diameters, respectively) was inserted into the bladder through the dome and secured with a purse-string suture. Body temperature was maintained at 37± 2°C (TCAT-2LV controller, Physitemp, ADInstruments Pty Ltd., Casttle Hill, Australia) throughout the experiment.

[0638] Cystometric experiment

[0639] Cystometric investigations were performed in anesthetized female rats after surgery. Physiological saline at room temperature was continuously infused into the bladder at a constant flow rate (2 mL/h) for a period of at least 30 min.

[0640] At the end of the cystometric experiments, animals were sacrificed by a lethal injection (1 mL) of sodium pentobarbital (54.7 mg/mL) (CAS n°76-74-4) followed by cervical dislocation.

[0641] Cystometric parameters

[0642] The cystometric parameters measured were:

[0643] Amplitude of micturition (AM), *i.e.* pressure between threshold pressure and Maximal pressure of micturition (mmHg),

[0644] Intercontraction interval (ICI), *i.e.* time between two subsequent micturitions (sec),

[0645] Micturition frequency (MF), *i.e.* number of micturition contractions /15 min (peaks/15 min).

[0646] Exclusion criteria

[0647] Two rats were excluded during the experiments: One was excluded as it presented with bladder hyperactivity during the saline intravesical infusion, and the other because the depth of anesthesia changed during the experiment inducing modifications of the cystometric profile.

[0648] Analysis of results

[0649] For each rat, values for AM and ICI were calculated as the mean of the last four or five micturitions during saline infusion. Values for MF were calculated as the mean of micturitions obtained for two intervals of 15 minutes during saline infusion.

[0650] Results are presented as mean values ± standard error of the mean (± sem). Figures and statistical analyses were performed using GraphPad Prism® (Version 4; GraphPad Software Inc., La Jolla, CA, USA).

[0651] Statistical comparisons of values (saline infusion) in the anti-CGRP antibody group *versus* the control antibody group were performed using unpaired Student *t*-test.

[0652] A $p<0.05$ was accepted for statistical significance.

[0653] **Results:**

[0654] As shown in FIG. 41, ICI was significantly greater and MF was significantly lower in the anti-CGRP Ab-treated group (FIGS. 41A and B respectively; $p<0.05$, unpaired Student *t*-test). No significant difference was observed for AM between groups (FIG. 41C, $p>0.05$, unpaired Student *t*-test).

[0655] These results suggest that anti-CGRP antibodies may be useful in preventing or alleviating overactive bladder, improving urinary continency and treatment of related urinary conditions.

Example 9 *Relief of neuropathic pain in rats*

[0656] Damage to the peripheral nerves often leads to chronic referred pain that is neuropathic in origin. This pain syndrome consists of sensitivity to external stimuli (e.g., mechanical and/or thermal) that are not normally noxious. Consequently, neuropathic pain is refractory to traditional analgesic approaches, making it difficult to treat. Experimentally, neuropathic pain can be modeled in animals via surgical trauma to peripheral nerves. The Chung model is one such system where neuropathic pain is induced by ligation of the spinal nerves of L5 and L6.

[0657] In this Example, a spinal nerve ligation was performed on male Sprague Dawley rats. They were tested for pain sensitivity on Day 13 (allodynia confirmation) and then again after each administration of Ab2 using the von Frey test of mechanical allodynia to assess possible anti-allodynic activity.

[0658] *Methods*

[0659] Male Sprague Dawley rats (Harlan Laboratories) weighing 200-225g at arrival, were unpacked and placed in cages. A visual health inspection was performed on each animal to include evaluation of the coat, extremities and orifices. Each animal was also examined for any abnormal signs in posture or movement. All animals were found to be in good health and were placed on study.

[0660] The rats were acclimated for a minimum of two days prior to the commencement of the experimental procedures, with the exception of randomization body weights which were collected the day following arrival. The animals were housed individually in clear polycarbonate conventional cages or clear polycarbonate microisolator cages with certified irradiated contact bedding. Food and water were provided *ad libitum*. Environmental controls were set to maintain temperatures of 18° to 26°C (64° to 79°F) with a relative humidity of 30% to 70%. A 12:12 hour light:dark cycle was maintained.

[0661] Rats were tested for baseline threshold using the von Frey filaments on Days -4 or -1 of acclimation.

[0662] On Day 0, animals underwent a spinal nerve ligation procedure. All surgeries were performed under aseptic conditions. Prior to surgeries, the rats were anesthetized. The back region was shaved and prepared for aseptic surgery. The rats were placed in ventral recumbence and an incision was made just left of midline at the L4 – S2 region. The left paraspinal muscles were separated from the spinous processes (L4 – S2). The L6-S1 facet joint were nipped and the transverse process gently trimmed to provide space to access theL4 & L5 spinal nerve. The left L5 and L6 spinal nerves were isolated and ligated with 6.0 silk sutures. The incision was then closed with appropriate suture material and skin wound clips. Post-operatively, Lactated Ringer's Solution (3.0 – 5.0 mL) was administered via subcutaneous injection to the animals.

[0663] All animals in Groups 1 and 2 received a von Frey test on Days -4 or -1, 13, 14, and 17. The measurement on Day 13 was taken pre-dose. The von Frey test for mechanical allodynia assesses anti-nociceptive properties of analgesic compounds. In this test, animals were first habituated to the testing chamber so they were calm enough for their pain threshold to be assessed. A technician blind to the treatment groups applied light pressure

to the left hind paw of the rat using a series of graded nylon filaments (von Frey filaments) of increasing diameter. The filaments were pressed perpendicularly against the ventral surface of the paw until they bent. When considered painful, the rat responds by withdrawing its paw. Threshold allodynia was determined using the Chaplan up-down method (Chaplan et al., J Neurosci Methods, 53:55-63, 1994), which provides the precise force for withdrawal for each rat using a psychophysical scale of testing.

[0664] Animals were allocated into two treatment groups on Day 13, based on von Frey scores. Any animal that had a von Frey score greater than 6g was excluded from the study. The mean von Frey scores for each group were reviewed to ensure that the mean values and standard deviation satisfied the assumption of homogeneity. Doses were administered by IP injection once on Day 13 (13 days after surgery) for Group 1 (Ab2) and Group 2 (negative control antibody) (11 animals in each group; Ab2 and negative control antibodies were administered at 10 mg/kg). Group 1 received an additional IV bolus (un-anesthetized) injection of Ab2 on Day 17 prior to behavioral testing.

[0665] Blood samples for plasma were taken on Day 17 for Group 1 and analyzed for Ab2 titer.

[0666] Outside of the expected surgical site observations and paw dragging associated with the Chung surgery, no abnormal observations were documented. Treatment appeared to have no adverse effect on overall animal health nor did it disrupt the normal weight gain expected in rats this age.

[0667] *Results*

[0668] All animals that underwent baseline testing prior to surgery on Day 0 had a von Frey score of 15 (not shown) indicating normal sensitivity. On Day 13 (prior to antibody administration), all animals had von Frey scores lower than 6g, indicating that sensitivity to external mechanical stimuli had developed, except for two animals which were removed from the study. Average von Frey scores at day 13 were less than 3 g (FIG. 42, left group of bars). Following testing on day 13, animals were administered Ab2 or a negative control antibody (10 mg/kg). On days 14 and 17, von Frey scores were again tested and were higher in the Ab2-treated animals than controls (FIG. 42, middle group of bars and right group of bars, respectively).

[0669] These results indicate that treatment with an anti-CGRP antibody such as Ab2 may help prevent or alleviate neuropathic pain.

Example 10 *First Experiment Assessing Effect of Anti-CGRP Antibody Administration on Analgesia (Tail Flick Model)*

[0670] Three different experiments (Examples 10-12) were conducted to assess the potential efficacy of an anti-CGRP antibody administration on analgesia or pain. In all of these experiments a rodent tail flick (also referred to as tail withdrawal) response model was used as the rodent tail flick response to radiant heat is a commonly used model to detect potentially useful analgesic agents. This assay is particularly useful to discriminate between centrally acting morphine-like analgesics (active) and non-opioid or peripherally acting anti-inflammatory agents (inactive). This animal model and methods and materials used therein are described below.

[0671] **Materials and Methods**

[0672] **Animals:** Male Sprague Dawley derived male rats weighing 150 ± 20 g.

[0673] **Test CGRP Antibody:** Ab2

[0674] **Vehicle:** 15 mM Histidine 250 mM Sorbitol, pH 5.5

[0675] **Analgesic Compound**: Morphine

[0676] **Tail Flick Response Procedures:** The time (seconds) required to elicit a tail flick response induced by focused radiant heat was measured as the pain threshold in groups of 10 Sprague Dawley derived male rats weighing 150 ± 20 g. Baseline testing for the tail flick response was done on Day 0. The rats that have a tail flick response of 3-5 seconds were included in the study and assigned to balanced treatment groups based on baseline tail flick responses. A 15 second cut was used to avoid tissue damage.

[0677] **Development of morphine tolerance**

[0678] Each of 3 groups of 10 Male Sprague Dawley rats were dosed 2 x daily via i.p. administration with saline vehicle (2 ml/kg) in the morning and evening. One of the 3 groups was in addition administered i.p. analgesic (morphine) at a dosage of 5 mg/kg 2 x daily for 7 consecutive days. A second of the 3 groups of rats was administered i.p. an anti-CGRP antibody according to the invention (Ab2) at a dosage of 10 mg/kg as a single

bolus on day 0. The rats in the different groups were then each tested for tail flick response once per day 30 min after the morning dose.

[0679] A one-way ANOVA followed by Dunnett's t-test is applied for comparison between the vehicle control and test-compound treated groups. $P<0.05$ is considered significant.

[0680] The results of these experiments are shown in Figure 43. The results therein indicate that the test CGRP antibody when administered at 10 mg/kg elicited significant long-lasting analgesic effect to a thermal pain stimulus. Terminal blood samples were taken from all the tested rats via cardiac puncture and later analyzed for Ab2 titer.

Example 11: *Second Tail Flick Experiment Assessing Effect of-CGRP Antibody on Analgesia) (Antibody Dose Titration)*

[0681] A second set of tail flick experiments were conducted to assess the effects of different anti-CGRP antibody dosages on analgesia using an anti- CGRP antibody according to the invention (Ab2). The rats used in these experiments are the same type as in the previous experiment and the tail flick protocol substantially the same. In this experiment analgesia was compared in different groups of animals administered different anti-CGRP antibody dosages in order to assess whether the dosage has an effect on analgesia. In the second set of experiments, five groups of test animals were compared as follows. A first control group of animals were each administered the vehicle alone (15 mM Histidine 250 mM Sorbitol, pH 5.5), 3 groups of animals were each administered different dosages of the same anti-CGRP antibody contained in the vehicle (Ab2, respectively administered at dosages of 1 mg/kg, 3 mg/kg or 10 mg/kg on Day 0), and a fifth group of animals was administered 10 mg/kg of a negative control antibody (anti-digitoxin antibody) also on Day 0.

[0682] The tail flick protocols were otherwise substantially effected as above-described. The results were again assessed using one-way ANOVA followed by Dunnett's t-test for comparison between the vehicle control, negative control antibody and test-CGRP antibody treated groups. $P<0.05$ is considered significant.

[0683] The results of these experiments are shown in Figure 44. It can be seen therefrom that the higher antibody dosages of the test compound (inventive Ab2 anti-

CGRP antibody) elicited better analgesic effects than the lower dosages. As anticipated the negative control antibody did not elicit a perceptible effect on analgesia relative to the control groups.

Example 12: Third Tail Flick Experiment Assessing Effect of Anti-CGRP Antibody/Morphine Co-administration on Analgesia

[0684] A third set of tail flick experiments were also conducted to assess the effects of anti-CGRP antibody/morphine co-administration on analgesia. In these experiments a first group of animals was administered the same vehicle alone at a dosage of 5 ml/kg. A second group of animals was administered morphine on days 1-10 at a dosage of 5 mg/kg, administered twice daily, wherein such animals were on Day 0 were also administered the anti-CGRP antibody Ab2 at a dosage of 10 mg/kg. A third group of animals was administered morphine on only days 1-4 again at a dosage concentration of 5 mg/kg, administered twice daily, and were further administered the Ab2 antibody on Day 0, at a dosage of 10 mg/kg. All administrations were i.p.

[0685] Tail flick experiments were effected in each of these groups of animals daily from Day 0-10. The results of these tail flick experiments were again assessed using one-way ANOVA followed by Dunnett's t-test for comparison between the vehicle control, negative control antibody and the test anti-CGRP antibody treated group. $P<0.05$ is considered significant.

[0686] The results of these comparisons are summarized in Figure 45. The Ab2-treated animals receiving a daily dose of morphine throughout the experiment exhibited morphine tolerance, and after day 5 the tail flick time had decreased almost to the level of vehicle-treated control animals. In contrast, in Ab2-treated animals receiving morphine only until day 4, the tail flick time improved on day 5 and remained improved until day 8. The results suggest that the administration of an anti-CGRP antibody may have analgesic effects even after onset of morphine tolerance, which may be more pronounced upon withdrawal of morphine.

Example 13 *Relief of visceral pain in rats*

[0687] Patients suffering from irritable bowel syndrome (IBS) demonstrate a lower visceral sensory threshold to colorectal balloon distension (Ritchie, Gut, 1973, 14:125-32). It has been suggested in IBS that there is heightened pain sensitivity of the brain-gut axis, with a normal pattern of activation. It has previously been shown that injection of trinitrobenzene sulfonic acid (TNBS) into the proximal colon provoked chronic colonic hypersensitivity, measured in conscious rats by a decreased pain threshold in response to colonic distension (Diop et al., J. Pharmacol. Exp. Ther., 2002, 302:1013-22). This chronic hypersensitivity was found in the distal non-inflamed colon and persisted for 21 days. It mimicked certain characteristics of IBS and so it can be used as a model to experimentally explore the pathophysiological aspects of this disorder. This assay is used to determine the potential antihypersensitive effects of compounds for TNBS-induced colonic hypersensitivity.

[0688] Several studies have implicated CGRP in visceral pain (Friese et al., Regul Pept 1997;70:1–7; Gschossmann et al., Neurogastroenterol Motil 2001;13:229–36; Julia and Bueno, Am J Physiol 1997;272:G141–6; Plourde et al., Am J Physiol 1997;273:G191–6). CGRP is the most abundant peptide of capsaicin sensitive afferent fibers of gastrointestinal origin, accounting for up to 80% of overall peptide immunoreactivity (Clague et al., Neurosci Lett 1985;56:63–8; Sternini et al., Gastroenterology 1987;93:852–62). Additionally, injection of CGRP induces colonic hypersensitivity in a TNBS model (Delafoy et al., 2006, Gut 55:940-5), which is reversed by a CGRP antagonist peptide (CGRP 8-37).

[0689] This example describes testing of an anti-CGRP antibody in a model of visceral pain (TNBS-induced chronic colonic hypersensitivity) in rats.

[0690] *Methods*

[0691] Male Sprague-Dawley rats, weighing 390 to 450 g the day of surgery were included in this study. They were housed in a temperature (19.5°C - 24.5°C) and relative humidity (45 % - 65 %) controlled room with a 12 h - light/dark cycle. Animals were housed 2 or 3 per cage and an acclimation period (at least 5 days) was observed before testing. Each rat was identified by tail markings. The study was performed according to

the guidelines of the Committee for Research and Ethical Issue of the I.A.S.P. (1983) and the European guidelines 2010/63/UE.

[0692] Colonic sensitivity was induced by surgical administration of Trinitrobenzene sulfonic acid (TNBS, 50 mg/kg) 7 days before behavioral testing. Fasted (24 hours) animals underwent surgery. Briefly, under anesthesia (Acepromazine 5 mg/kg / Ketamine 30 mg/kg), injection of TNBS (50 mg/kg, 1 ml/kg) was performed into the proximal part of the colon (1 cm from the caecum). After surgery, animals were returned to their cages in a regulated environment, and fed ad libitum until the testing day, 7 days later. "Naïve" animals (rats without surgery) were placed in the same housing conditions.

[0693] Animals were administered the anti-CGRP antibody Ab2 or a negative control antibody (both at 10 mg/kg) intravenously 24 hours prior to determination of colonic threshold. Three groups of rats were included in this study:

[0694] Group 1: A "Naïve" group composed of animals that did not undergo surgery or TNBS treatment on D-7 and were treated with the control antibody 24 hrs prior (i.e. D-1) to testing (i.e. measurements of the colonic distention threshold on D0) (n=7).

[0695] Group 2: A "TNBS" group composed of animals that underwent surgery on D-7 and were treated with control antibody (24 hrs prior (i.e. D-1) to testing (i.e. measurements of the colonic distention threshold on D0) (n=8).

[0696] Group 3: A "Treated" group composed of animals that underwent surgery on D-7 and were treated with Ab2 24 hrs prior (i.e. D-1) to testing day (i.e. measurements of the colonic distention threshold on D0) (n=8).

[0697] Seven days (D7) after TNBS injection, colonic sensitivity was assessed by measuring the intra-colonic pressure required to induce a behavioral response during colonic distension due to the inflation of a balloon introduced in the colon. The tests were conducted by a blinded experimenter. This response is characterized by an elevation of the hind part of the animal body and a clearly visible abdominal contraction corresponding to severe contractions (Al Chaer et al., Gastroenterology 2000, 119:1276-1285) and used as a pain marker (Bourdu et al., Gastroenterology. 2005:128, 1996-2008). The balloon (5 cm) was inserted intrarectally in a minimally invasive manner to 10 cm from the anus of fasted (24h) vigil animals, and the catheter was taped to the base of the tail. Rats were then placed

in the middle of a plexiglass box and the catheter was connected to an electronic barostat apparatus. After a 30 min-acclimation period with the inserted balloon, colonic pressure was gradually increased by 5 mmHg steps every 30 sec from 5 to 75 mmHg (cut off) until pain behavior is evidenced. Four determinations were performed, 30 min, 50 min, 70 min and 90 min after balloon insertion.

[0698] Using the data from each test, the percentage of activity on colonic hypersensitivity induced by the intracolonic administration of TNBS was calculated as follows

$$(Activity\,percentage)_{Treated}=\frac{Distentionthreshold_{Treated}-Distentionthreshold_{TNBS}}{Distentionthreshold_{Naive}-Distentionthreshold_{TNBS}}x100$$

[0699] *Distention threshold*$_{Treated}$ is the arithmetic mean of the values for the "Treated" group; *Distention threshold*$_{TNBS}$ is the arithmetic mean of the values for the "TNBS" group; and *Distention threshold*$_{Naive}$ is the arithmetic mean of the values for the "Naïve" group.

[0700] *Results*

[0701] The ability of an anti-CGRP antibody to alleviate visceral pain was tested in a rat model in which chronic colonic hypersensitivity was induced by administration of TNBS. Visceral pain was quantified by measuring the colonic distension threshold, i.e., the amount of abdominal pressure that the animals could tolerate before exhibiting a behavioral response (muscle contraction). Higher colonic distension threshold values indicate less sensitivity. As expected, TNBS treatment resulted in greatly decreased the colonic distension threshold compared to naïve animals (FIG. 46, compare middle bar (TNBS treated) and left bar (naïve)). Ab2 administration improved the colonic distension threshold compared to control animals (FIG. 46, compare right bar (Ab2 treated) and middle bar (control)). The improvement from Ab2 administration was statistically significant ($p < 0.05$ Student's t-test, comparison to TNBS + Negative control group). The antihypersensitive activity of Ab2 was computed to be 27% (indicative of the degree of relief of the TNBS-induced hypersensitivity).

[0702] These results suggest that anti-CGRP antibodies may be useful in preventing or alleviating visceral pain.

CLAIMS

1.) An isolated anti-human CGRP antibody or antibody fragment comprising (i) a variable light (V_L) chain polypeptide comprising a V_L complementarity determining region 1 (CDR1) of SEQ ID NO:55, a V_L complementarity determining region 2 (CDR2) of SEQ ID NO:56, a V_L complementarity determining region 3 (CDR3) of SEQ ID NO:57; and a variable heavy (V_H) chain polypeptide comprising a V_H CDR1 of SEQ ID NO:58, a V_H CDR2 of SEQ ID NO:59 and a V_H CDR3 of SEQ ID NO:60.

2.) The isolated anti-human CGRP antibody or antibody fragment according to claim 1, wherein said anti-human CGRP antibody or antibody fragment comprises:

(i) a V_H chain polypeptide having the amino acid sequence set forth in SEQ ID NO: 53, or a variant thereof that exhibits at least 90%, at least 95%, at least 98% or at least 99% sequence identity therewith; and/or

(ii) a V_L chain polypeptide having the amino acid sequence set forth in SEQ ID NO: 51, or a variant thereof that exhibits at least 90%, at least 95%, at least 98% or at least 99% sequence identity therewith,

wherein one or more of said framework (FR) residues are optionally 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 chain polypeptides have been derived or by a conservative amino acid substitution, preferably at most 1 or 2 of the residues in the CDRs of said V_L chain polypeptide sequence and/or at most 1 or 2 of the residues in the CDRs of said V_H chain polypeptide sequence are modified.

3.) The isolated anti-human CGRP antibody or antibody fragment according to claim 1, wherein said anti-human CGRP antibody or antibody fragment comprises:

(i) a V_L chain polypeptide having the amino acid sequence of SEQ ID NO:51 and a V_H chain polypeptide having the amino acid sequence of SEQ ID NO:53;

(ii) a light chain having the amino acid sequence of SEQ ID NO:52 and a heavy chain having the amino acid sequence of SEQ ID NO:54.

4.) The isolated anti-human CGRP antibody or antibody fragment according to any one of claims 1 to 3, which:

(i) is aglycosylated;

(ii) is glycosylated, but only contains only mannose residues;

(iii) is not N-glycosylated;

(iv) contains an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation;

(v) is a humanized antibody, a chimeric antibody, a single chain antibody or a monovalent antibody;

(vi) is an antibody fragment selected from a Fab fragment, a Fab' fragment, a F(ab')2 fragment, or a monovalent antibody;

(vii) is directly or indirectly attached to a detectable label or therapeutic agent;

(viii) 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};

(ix) inhibits the association of CGRP with a CGRP-R and/or multimers thereof, one or more additional proteins in a CGRP-CGRP-R complex, and/or antagonizes the biological effects thereof;

(x) further comprises an effector moiety that is a detectable moiety or a functional moiety, wherein said detectable moiety is optionally a fluorescent dye, an enzyme, a substrate, a bioluminescent material, a radioactive material, or a chemiluminescent material and said functional moiety optionally is streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, or a radioactive material; or

(xi) comprises a human F_c that is derived from IgG1, IgG2, IgG3, or IgG4.

5.) The isolated anti-human CGRP antibody or antibody fragment according to any one of claims 1 to 4, which specifically binds to CGRP expressing human cells and/or binds to circulating soluble CGRP molecules in vivo and/or specifically binds to CGRP expressed on or by human cells in a patient with a disease associated with cells that bind CGRP, wherein the disease is selected from migraine with aura, migraine without aura, a condition with CGRP-associated pain, weight loss, cancer or tumors, overactive bladder, urinary incontinence, pruritus, psoriasis, ulcer, a cardiac condition, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, migraines, chronic migraines, frequent episodic migraines, menstrual migraines, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysmal hemicrania, secondary headaches due to an underlying structural problem in the head, secondary headaches due to an underlying problem in the neck, cranial neuralgia, sinus headaches (such as for example associated with sinusitis), allergy-induced headaches, allergy-induced migraines, pain, TMJ, temporomandibular jaw disorders, inflammatory pain, visceral pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary bone cancer pain, metastatic bone cancer pain, fracture pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, pain associated with sickle cell crises, hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptive pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, osteoarthritis pain, rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, 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, and pancreatitis; preferably wherein the disease is selected from pain, visceral pain, TMJ, temporomandibular jaw disorders, headache, overactive bladder, urinary incontinence, cluster headache and migraine; more preferably, wherein the disease is migraine selected from migraine with aura, migraine without aura, chronic migraine, frequent episodic migraines, or menstrual migraines.

6.) A nucleic acid sequence or nucleic acid sequences encoding the anti-human CGRP antibody or antibody fragment of any one of claims 1 to 5, wherein the nucleic acid sequence or sequences are optionally comprised of yeast or human preferred codons.

7.) A vector comprising the nucleic acid sequence or sequences of claim 6, wherein the vector is optionally a plasmid or recombinant viral vector.

8.) A cultured or recombinant cell that expresses an antibody or antibody fragment encoded by the nucleic acid sequence or sequences of claim 6 and/or the vector of claim 7, wherein the cell is optionally selected from a yeast, mammalian, bacterial, fungal, or insect cell, wherein preferably the cell is a diploidal yeast cell such as a Pichia yeast.

9.) An anti-human CGRP antibody or antibody fragment of any one of claims 1 to 5 for use in the treatment of a disease or condition treatable by the administration of a therapeutically effective amount of a CGRP antagonist and/or ameliorating or reducing symptoms of a disease or condition treatable by the administration of a CGRP antagonist, wherein the disease or condition is associated with CGRP expressing cells, preferably cells with increased CGRP expression, which is optionally selected from migraine with aura, migraine without aura, weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, migraine, chronic migraine, frequent episodic migraines, menstrual migraines, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysmal hemicrania, secondary headaches due to an underlying structural problem in the head, secondary headaches due to an underlying problem in the neck, cranial neuralgia, sinus headaches (such as for example associated with sinusitis), allergy-induced headaches, allergy-induced migraines, pain, inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary bone cancer pain, metastatic bone cancer pain, fracture pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, pain associated with sickle cell crises, hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptive pain, trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, fibromyalgia, ovarialgia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis pain, rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, 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, wherein the disease is preferably selected from overactive bladder; urinary incontinence; pain; chronic pain; neurogenic inflammation; inflammatory pain; neuropathic pain; eye pain; tooth pain; post-surgical pain, trauma related pain, diabetes; non-insulin dependent diabetes mellitus and other inflammatory autoimmune disorders, vascular disorders; inflammation; arthritis; bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases, pruritus, neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and dysmenorrhea, wherein the disease is more preferably selected from pain, overactive bladder, urinary incontinence, headache or migraine.

10.) The antibody of claim 9, which is to be administered with another therapeutic agent selected from an analgesic, an anti-histamine, an anti-inflammatory agent, an antibiotic, a chemotherapeutic, an immunosuppressant, a cytokine, an anti-proliferative, an antiemetic or a cytotoxin,

wherein the analgesic is optionally an NSAID, an opioid analgesic, an antibody or antibody fragment, or a non-antibody biologic,

wherein the NSAID is preferably selected from a cyclooxygenase 1 and/or cyclooxygenase 2 inhibitor; propionic acid derivatives including ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; acetic acid derivatives including tolmetin and sulindac; fenamic acid derivatives including mefenamic acid and meclofenamic acid; biphenylcarboxylic acid derivatives including diflunisal and flufenisal; and oxicams including piroxicam, sudoxicam, and isoxicam,

wherein the analgesic is preferably selected from a phenanthrene; a phenylheptylamine; a phenylpiperidine; a morphinan; and a benzomorphan compound,

wherein the opioid analgesic is preferably selected from codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil,

buprenorphine, butorphanol, fentanyl, sufentanil, meperidine, methadone, nalbuphine, propoxyphene, pentazocine or pharmaceutically acceptable salts thereof, and morphine or a morphine derivative or pharmaceutically acceptable salts thereof, and

wherein the antibody or antibody fragment is preferably a NGF antibody or antibody fragment.

11.) A method of in vivo imaging that detects the presence of cells expressing CGRP comprising administering a diagnostically effective amount of at least one anti-human CGRP antibody or antibody fragment according to any one of claims 1 to 5, wherein said administration optionally further includes the administration of a radionuclide or fluorophore that facilitates detection of the antibody at CGRP expressing disease sites and wherein the results are optionally used to facilitate design of an appropriate therapeutic regimen.

12.) A method of making the antibody or antibody fragment of any one of claims 1 to 5 in a polyploid yeast culture that stably expresses and secretes into the culture medium at least 10-25 mg/liter of said antibody, comprising:

(i) introducing at least one expression vector containing one or more heterologous polynucleotides encoding said antibody operably linked to a promoter and a signal sequence into a haploid yeast cell;

(ii) producing by mating or spheroplast fusion a polyploidal yeast from said first and/or second haploid yeast cell;

(iii) selecting polyploidal yeast cells that stably express said antibody; and

(iv) producing stable polyploidal yeast cultures from said polyploidal yeast cells that stably express said antibody into the culture medium,

wherein said yeast is optionally a species of Pichia that is selected from *Pichia pastoris*, *Pichia methanolica* or *Hansenula polymorpha* (*Pichia angusta*), wherein the species of Pichia is preferably *Pichia pastoris*.

13.) The method of claim 12, wherein said heterologous polynucleotide comprises a sequence encoding the polypeptides contained in SEQ ID NO:51 and SEQ ID NO:53.

14.) A pharmaceutical or diagnostic composition containing at least one anti-human CGRP antibody or fragment according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier, wherein said composition optionally further comprises at least one stabilizer and is optionally lyophilized.