

Treatment of opioid-induced pain

#### Related Applications

The present application claims priority to U.S. Prov. Appl. No. 63/484,850, filed on February 14, 2023,  
5 the contents of which are incorporated by reference in their entirety.

#### SEQUENCE LISTING DISCLOSURE

The contents of the electronic sequence listing (1143257o010013.xml; Size: 963,036 bytes; and Date  
of Creation: February 2, 2024) is herein incorporated by reference in its entirety.

#### 10 Field of the invention

The present invention relates to a method of treatment and/or prevention of opioid-induced pain,  
such as opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced  
allodynia (OIA) by administration of an antibody and/or antigen-binding fragment thereof, preferably  
a humanized, chimerized, and human antibody and/or antigen-binding fragment thereof, wherein  
15 such antibody and/or antigen-binding fragment thereof specifically bind to Pituitary Adenylate  
Cyclase-Activating Polypeptide ("PACAP").

#### Background of the invention

Pituitary Adenylate Cyclase-Activating Polypeptide ("PACAP") is a member of the secretin/vasoactive  
20 intestinal peptide ("VIP")/growth hormone-releasing hormone ("GHRH") family. PACAP is a  
multifunctional vasodilatory peptide that exists in two  $\alpha$ -amidated active forms, one with 38 amino  
acids (PACAP38; SEQ ID NO: 1241) and the other with 27 amino acids (PACAP27; SEQ ID NO: 1242).  
Both peptides have the same N-terminal 27 amino acids and are synthesized from the same precursor  
protein, preproPACAP (See, Moody et al., *Curr. Opin. Endocrinol. Diabetes Obes.*, 18(1):61-67, 2011).  
25 PACAP38 is the more prevalent active form, representing up to 90% of PACAP forms in mammalian  
tissues (See, Kaiser and Russo, *Neuropeptides*, 47:451-461, 2013). The sequence of PACAP38 is  
identical in all mammals and differs from the avian and amphibian orthologs by only one amino acid  
(See, Vaudry et al., *Pharmacol. Rev.*, 52:269-324, 2000). The secretin/VIP/GHRH family includes  
mammalian peptide histidine methionine ("PHM"), secretin, glucagon, glucagon-like peptide-1  
30 ("GLP1"), glucagon-like peptide-2 ("GLP2"), glucose-dependent-insulinotropic-polypeptide ("GIP"),  
and growth-hormone-releasing-factor ("GRF"). PACAP27 has 68% sequence identity to VIP at the  
amino acid level (See, Vaudry et al., *Pharmacol. Rev.*, 52:269-324, 2000).

PACAP is widely distributed in the brain and peripheral organs, e.g., the endocrine system, gonads,  
sympathetic neurons, respiratory system, gastrointestinal tract, cardiovascular system, and urogenital  
35 tracts (See, Schytz et al., *Neurotherapeutics*, 7:191-196, 2010). In particular, PACAP is expressed

throughout the nervous system, including the trigeminovascular system, trigeminal ganglia, spinal cord, hypothalamus, and pituitary. PACAP also has roles in neurodevelopment, neuroprotection, neuromodulation, neurogenic inflammation, and nociception with multiple actions (See, *Neuropeptides*, 47:451-461, 2013).

- 5 Consistent with its widespread distribution, PACAP exerts pleiotropic effects including modulation of neurotransmitter release, vasodilation, bronchodilation, and activation of intestinal motility, increase of insulin and histamine secretion, as well as stimulation of cell proliferation and/or differentiation. PACAP has been shown to act as a hormone, a neurohormone, a neurotransmitter, and a trophic factor in a number of tissues (Vaudry et al., *Pharmacological Rev.*, 52(2):269-324, 2000).
- 10 The biological effects of PACAP are mediated via three different G-protein coupled receptors: PAC1-R, vasoactive intestinal peptide receptor type 1 ("VPAC1-R"), and vasoactive intestinal peptide receptor type 2 ("VPAC2-R"). These receptors are expressed in diverse tissues. PAC1-R is particularly abundant in the nervous system (e.g., olfactory bulb, thalamus, hypothalamus, cerebellum, and spinal dorsal horn), pituitary, and adrenal glands. By contrast, VPAC1-R and VPAC2-R are expressed mainly
- 15 in the lung, liver, and testis, although they have been detected in other tissues as well. VPAC1-R expression has been detected in the nervous system (e.g., cerebral cortex and hippocampus), smooth muscle cells of lung, liver, intestine, megakaryocytes, and platelets. VPAC1-R associates with receptor-associated membrane protein ("RAMP", specifically, RAMP2) (See, Christopoulos et al., *J. Biol. Chem.*, 278:3293-3297, 2002). VPAC2-R expression profile includes the nervous (e.g., thalamus, hippocampus,
- 20 brain stem, and dorsal root ganglia ("DRG")), cardiovascular system, gastrointestinal system, pancreas, and reproductive systems (See, Usdin et al., *Endocrin.*, 135:2662-2680, 1994; Sheward et al., *Neurosci.*, 67:409-418, 1995).

PAC1-R is selective for PACAP38 and PACAP27. In particular, PAC1-R binds to PACAP with 100-1000-fold greater affinity than VIP, i.e.,  $K_D \sim 0.5$  nM for PACAP27/PACAP38 vs.  $K_D \sim 500$  nM for VIP.

- 25 Conversely, VPAC1-R and VPAC2-R have equal affinities for PACAP and VIP ( $K_D \sim 1$  nM) (See, Schytz et al., 2010). An antibody has been developed that binds to PAC1-R (See United States Patent Application Publication No. 20160251432).

Upon activation, these receptors are all capable of causing downstream production of cyclic adenosine monophosphate ("cAMP"), and/or activation of phospholipase C ("PLC"), and/or modulation of

- 30 phospholipase D ("PLD"). In particular, PAC1-R is coupled to dual signal transduction pathways acting through cAMP and  $Ca^{2+}$ , whereas VPAC1-R and VPAC2-R are coupled principally to adenylyl cyclase. PAC1-R is coupled to  $G_s$  protein, which activates adenylyl cyclase to form cAMP that in turn activates protein kinase A. PAC1-R also couples to  $G_q$  and thereby activates PLC, which produces inositol phosphate, which increases cytosolic calcium release from intra-cellular calcium stores. There is some



evidence for a role of PAC1-R in PLD activation (See, McCulloch et al., *Ann. N. Y. Acad. Sci.*, 921:175-185, 2000). It has also been reported that PACAP signalling pathway modulation results in the elevation of intra-cellular sodium levels via activation of nonselective cation channels (See, Roy et al., *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, 304(12):R1070-R1084, 2013).

PACAP is hypothesized to play a role in a multitude of diseases and disorders, including but not limited to migraine, headache, and pain, though such a role for PACAP has not been clinically demonstrated. Migraines are believed to have a neurovascular component. Migraines affect 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. A role for PACAP in migraine has been supported by several observations: (1) plasma levels of PACAP are elevated during migraine attacks (ictal), as compared to interictal levels, in humans (See Tuka et al., *Cephalalgia*, 33(13):1085-1095, 2013); (2) an infusion of PACAP38 triggered headaches in healthy subjects, and headaches followed by migraine-like attacks in migraineurs (See Schytz et al., *Brain*, 132:16-25, 2009; and Amin et al., *Brain*, 137:779-794, 2014, respectively); (3) PACAP-induced vasodilation may play a role in neurogenic inflammation (See Kaiser and Russo, *Neuropeptides*, 47:451-461, 2013); and (4) PACAP-induced migraines are associated with photophobia, phonophobia, nausea, and respond to triptans (See Amin et al., *Brain*, 32:140-149, 2012). PACAP has also been shown to induce vasodilation, photophobia, as well as mast cell degranulation and neuronal activation (See, Markovics et al., *Neurobiology of Disease*, 45:633-644, 2012; Baun et al., *Cephalalgia*, 32(4):337-345, 2012; Chan et al., *Pharmacology & Therapeutics*, 129:332-351, 2011).

PACAP and PACAP receptors have also been suggested to modulate inflammatory and neuropathic pain and have been implicated in both pronociception and antinociception (See, Davis-Taber et al., *J. Pain*, 9(5):449-56, 2008). PACAP has also been reported to be required for spinal desensitization and the induction of neuropathic pain (See, Mabuchi et al., *J. Neurosci.*, 24(33):7283-91, 2004). Additionally, morphine withdrawal behavior is reportedly modified in PACAP-receptor deficient mice further suggesting the role of PACAP in morphine withdrawal anxiolytic response (See, Martin et al., *Mol. Brain Res.*, 110(1):109-18, 2003).

One effective treatment of pain is through the administration of certain narcotics, such as opioids, or non-steroidal anti-inflammatory drugs ("NSAIDs"). However, the administration of these treatments often has 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. A further negative consequence of treating migraine or other pain with opioids is the risk of developing opioid-induced pain, such as opioid-induced hyperalgesia (OIH) and opioid-induced allodynia (OIA). Opioid-induced hyperalgesia (OIH) is defined as a state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a

5 paradoxical response whereby a patient receiving opioids for the treatment of pain could become more sensitive to certain painful stimuli. The type of pain experienced might be the same as the underlying pain originally treated with the opioids or might be different from the original underlying pain. (See, Lee, *Pain Physician*, 14:145-161, 2011).

10 In an LC-MS study, PACAP, Vasoactive intestinal peptide (VIP), and Secretogranin (SCG) were identified as common peptides involved in both migraine and opioid-induced hyperalgesia (See, Anapindi, *Molecular & Cellular Proteomics* 18, 2447–2458, 2019). Administration of M65, a PAC1 receptor antagonist, was found to reverse chronic migraine and OIH in a mouse model.

Opioid-induced pain, such as opioid-induced chronic migraine, OIH, and OIA, is a common problem to

15 patients administered opioids for the treatment of pain. The current treatment applied for opioid-induced pain is to gradually reduce the opioid treatment regimen and possibly to completely stop the opioid treatment. Such reduction or stop of opioid treatment may result in relief from the opioid-induced pain, however, also may leave the original pain untreated, resulting in suboptimal pain alleviation for the patient. Thus, there is an unmet need for treatment of opioid-induced pain to

20 provide relief of the pain experienced and optimally to allow for continued and optimal pain relief for the patient.

#### Summary of the Invention

The inventors of the present disclosure have surprisingly found that administration of an anti-PACAP

25 antibody and/or antigen-binding fragment thereof to a subject suffering from opioid-induced pain provides pain relief for the patients. As demonstrated by the examples of the present disclosure, administration of an anti-PACAP antibody and/or antigen-binding fragment thereof to a subject suffering from opioid-induced pain provided full attenuation of the opioid-induced pain, even when tested several days post administration.

30 Thus in one aspect, the present disclosure provides a method of treating, ameliorating and/or preventing pain, such as hyperalgesia or allodynia, said method comprising administering to a subject in need thereof an effective amount of an anti-Pituitary Adenylate Cyclase-Activating Polypeptide

("PACAP") antibody and/or antigen-binding fragment thereof. In one embodiment, the pain is resulting from the subject being exposed to an opioid, such as opioid-induced pain.

Thus in one aspect, the present disclosure provides a method of treating, ameliorating and/or preventing opioid-induced pain, comprising administering to a subject in need thereof an effective amount of an anti-Pituitary Adenylate Cyclase-Activating Polypeptide ("PACAP") antibody as disclosed herein. In one embodiment, the opioid-induced pain is selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

In another aspect of the invention the present disclosure provides a method of treating, ameliorating and/or preventing medication overuse headache (MOH), comprising administering to a subject in the need thereof an effective amount an anti-PACAP antibody as disclosed herein.

#### Definitions

Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP): As used herein, unless stated otherwise PACAP includes any mammalian form of PACAP, and in particular encompasses the following Homo sapiens PACAP27 and Homo sapiens PACAP38 amino acid sequences:

PACAP38: HSDGIFTDSYSRYRKQMAVKKYLA AVL GKRYKQ RVKNK (SEQ ID NO: 1241), wherein the C-terminal lysine is amidated; but also any mutants, splice variants, isoforms, orthologs, homologs, and variants of this sequence.

PACAP27: HSDGIFTDSYSRYRKQMAVKKYLA AVL (SEQ ID NO: 1242), wherein the C-terminal leucine is amidated; but also any mutants, splice variants, isoforms, orthologs, homologs, and variants of this sequence.

"Photophobia" herein refers to a symptom of abnormal intolerance to visual perception of light, sometimes additionally defined by abnormal or irrational fear of light, or by presence of actual physical photosensitivity of the eyes. In the present invention photophobia includes in particular light aversion associated with migraine and other neurological causes of light aversive behavior that can trigger a migraine.

The term "opioid-induced chronic migraine", as used herein, refers to a condition wherein a patient receiving an opioid for the treatment of an original pain, such as for the treatment of headache or migraine, is experiencing or developing chronic migraine. Chronic migraine is defined as having at least 15 headache days a month, with at least 8 days of having headaches with migraine features, for more

- than 3 months. The term “migraine” refers to a complex and disabling neurological disorder that may progress during four stages: prodrome, aura, headache, and postdrome. A migraine is defined by the International Headache Society as a headache that lasts for 4-72 hours and is characterized by at least two of the following: unilateral localization, pulsating quality, moderate to severe pain intensity; and
- 5   aggravation by movement such as walking. In addition, the headache must be accompanied by at least one of the following: nausea and/or vomiting, photophobia, or phonophobia. A migraine may also be accompanied by aura, which typically precedes the headache during the premonition or prodrome phase, and often results in visual changes, e.g., a scintillating scotoma that moves across the visual field. The prodrome may also be accompanied by other symptoms, e.g., fatigue, gastrointestinal
- 10   issues, and mood changes. A migraineur is often incapacitated for extended periods of time. The postdrome is the final phase and occurs after the attack, during which time the migraineur may feel exhausted or mildly euphoric. The chronic migraine may be selected from migraine with aura, migraine without aura, and hemiplegic migraine. The chronic migraine may result from administration of an opioid for treatment of pain, such as headache and/or migraine, resulting in
- 15   opioid-induced exacerbated migraine, such as migraine resulting from exposure to low doses of a migraine trigger which would usually not result in migraine, however, due to the opioid-treatment, the migraine response is exacerbated resulting in an increase in the number of days with migraine and development of chronic migraine.
- 20   The term “opioid-overuse headache”, as used herein, refers to a condition wherein a patient receiving an opioid for the treatment of an original pain, such as for the treatment of headache or migraine, is experiencing or developing headache, such as headaches of increase intensity, duration and/or frequency of recurrence.
- 25   The term “opioid-induced hyperalgesia” (OIH, also called opioid-induced abnormal pain sensitivity), as used herein, refers to a state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of an original pain becomes more sensitive to certain painful stimuli. The type of pain experienced in OIH might be the same as the original pain initially treated by administration of an
- 30   opioid or might be different from the original pain. In one embodiment, the OIH is characterized by diffuse pain, pain which is less defined in quality, pain which quality is harder to define, original pain which affects a broader area than was originally affected, increased pain intensity without the underlying medical condition for the original pain having been worsened, pain which extends to other

areas of distribution from the original pain, and/or pain which is different from the original pain and which has developed without a specific diagnosis.

5 The term "opioid-induced allodynia" (OIA), as used herein, refers to a condition wherein a patient receiving an opioid for the treatment of an original pain is experiencing pain from stimulations which were not painful before, such as for example wherein stroking the skin with a cotton ball produces a painful reaction.

10 The term "headache" refers to pain in any region of the head. Headaches may occur on one or both sides of the head, be isolated to a certain location, radiate across the head from one point, or have a vise-like quality. A headache may be a sharp pain, throbbing sensation or dull ache. Headaches may appear gradually or suddenly, and they may last from less than an hour up to several days.

The term "opioid analgesic" herein refers to all drugs, natural or synthetic, with morphine-like actions.  
15 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,  
20 nalbuphine, propoxyphene, and pentazocine, or pharmaceutically acceptable salts thereof.

The term "medication overuse headache" (MOH) a secondary disorder caused by excessive use of acute medications as defined in ICHD-3 8.2. MOH is defined as i.a. a headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of  
25 regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than 3 months. The subjects are diagnosed according to the following criteria a) headache occurring on  $\geq 15$  days/month in a patient with a pre-existing headache disorder and b) regular overuse for  $>3$  months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, and c) not better accounted for by  
30 another ICHD-3 diagnosis.

As used herein, "treatment" refers to an approach for obtaining beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: improvement in any aspect of the opioid-induced pain. For example in the

context of headache or migraine treatment this includes lessening severity, alleviation of pain intensity, and other associated symptoms, reducing frequency of recurrence, increasing the quality of life of those suffering from the headache, and decreasing dose of other medications required to treat the headache. For migraine, other associated symptoms include, but are not limited to, nausea,  
5 vomiting, and sensitivity to light, sound, and/or movement.

"Prevention", "reducing incidence", or "prophylaxis" refers to reducing the probability of development of a particular disease, condition, symptom, or disorder (the terms disease, condition, and disorder are used interchangeably throughout the application). The terms are used  
10 interchangeably herein. In the present invention, prevention of the given disease may be achieved by prophylactically administering the anti-PACAP antibody and/or antigen-binding fragment thereof to a subject who is about to receive an opioid treatment, such as a subject who is about to receive an opioid treatment and who is considered at risk of developing opioid-induced pain. The method of treatment as herein disclosed may also be used for delaying the development of opioid induced pain,  
15 such as "delaying" the development of migraine or headache, which means to defer, hinder, slow, retard, stabilize, and/or postpone progression of the condition or disease. This delay can be of varying lengths of time, depending on the history of the condition or disease and/or individuals being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop opioid-induced pain. A method that "delays"  
20 development of the symptom is a method that reduces probability of developing the symptom in a given time frame and/or reduces extent of the symptoms in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a statistically significant number of subjects.

"Ameliorating" refers to a lessening or improvement of one or more symptoms of the condition, e.g., opioid-induced pain as compared to not administering an anti-PACAP antagonist antibody. "Ameliorating" also refers to any of reducing severity for a particular disease, condition, symptom, or disorder (the terms disease, condition, and disorder are used interchangeably throughout the application). Reduction in severity includes reducing drugs and/or therapies generally used for the  
25 condition by, for example, reducing the need for, amount of, and/or exposure to drugs or therapies. Reduction in severity also includes reducing the duration, and/or frequency of the particular condition, symptom, or disorder (including, for example, delaying or increasing time to next episodic attack in an individual). The method of treatment as herein disclosed may also be used for controlling opioid-induced pain, such as "controlling opioid-induced chronic migraine" which refers to maintaining or  
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reducing severity or duration of one or more symptoms of the condition, e.g., headache or migraine or frequency of headache or migraine attacks in an individual (as compared to the level before treatment). For example, the duration or severity of head pain, or frequency of attacks, is reduced by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, in the individual as compared to the level before treatment. The reduction in the duration or severity of head pain, or frequency of attacks can last for any length of time, e.g., 2 weeks, 4 weeks (1 month), 8 weeks (2 months), 16 weeks (3 months), 4 months, 5 months, 6 months, 9 months, 12 months, etc.

As used herein, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological, and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as reducing pain intensity, duration, or frequency of headache attack, and decreasing one or more symptoms resulting from headache (biochemical, histological, and/or behavioral), including its complications and intermediate pathological phenotypes presenting during development of the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication, and/or delaying the progression of the disease of patients. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish preventive, prophylactic, or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective dosage" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

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. 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.

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.

Chimeric antibodies may be made by recombinant means by combining the V<sub>L</sub> and V<sub>H</sub> regions, 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.

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.

The general structure of antibodies in vertebrates now is well understood. See Edelman, G. M., Ann. N.Y. Acad. Sci., 190:5 (1971). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 Daltons (the "light chain"), and two identical heavy chains of molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y"



configuration wherein the light chains bracket the heavy chains starting at the mouth of the “Y” configuration. The “branch” portion of the “Y” configuration is designated the Fab region; the stem portion of the “Y” configuration is designated the FC region. The amino acid sequence orientation runs from the N-terminal end at the top of the “Y” configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

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  $\gamma$ ,  $\mu$ ,  $\alpha$ ,  $\delta$ , and  $\epsilon$  (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 (See Kabat, E. A., Structural Concepts in Immunology and Immunochemistry, 2nd Ed., p. 413-436, New York, NY: Holt, Rinehart, Winston (1976)), and other cellular responses (See Andrews et al., Clinical Immunology, pp. 1-18, W. B. Sanders, Philadelphia, PA (1980); Kohl et al., Immunology, 48:187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either  $\kappa$  (kappa) or  $\lambda$  (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.

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.

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 et al., Sequences of Proteins of Immunological Interest, 4th ed., Bethesda, MD: U.S. Dept. of Health and Human Services, Public Health

Service, National Institutes of Health (1987)). These expressions include the hypervariable regions as defined by Kabat et al., (Sequences of Proteins of Immunological Interest, NIH Publication No. 91-3242, Bethesda, MD: U.S. Dept. of Health and Human Services, National Institutes of Health (1983)) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, *J. Mol. Biol.*, 5 196:901-917, 1987). The CDRs in each chain are held in close proximity by framework regions ("FRs") 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") that represent the critical contact residues used by the CDR in the antibody-antigen interaction. (See, Kashmiri et al., *Methods*, 36(1):25-34, 2005).

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An "epitope" or "binding site" is an area or region on an antigen to which an antigen-binding peptide (such as an antibody) specifically binds. A protein epitope may comprise amino acid residues directly involved in the binding (also called immunodominant component of the epitope) and other amino acid residues, which are not directly involved in the binding, such as amino acid residues that are 15 effectively blocked by the specifically antigen binding peptide (in other words, the amino acid residue is within the "footprint" of the specifically antigen binding peptide). The term epitope herein includes both types of amino acid binding sites in any particular region of PACAP, i.e., PACAP38 and PACAP27, that specifically binds to an anti-PACAP antibody. PACAP may comprise a number of different epitopes, which may include, without limitation, (1) linear peptide antigenic determinants, (2) 20 conformational antigenic determinants that consist of one or more non-contiguous amino acids located near each other in a mature PACAP conformation; and (3) post-translational antigenic determinants that consist, either in whole or part, of molecular structures covalently attached to a PACAP protein such as carbohydrate groups. In particular, the term "epitope" includes the specific residues in a protein or peptide, e.g., PACAP, which are involved in the binding of an antibody to such 25 protein or peptide as determined by known and accepted methods such as alanine scanning techniques. Such methods are exemplified herein.

The phrase that an antibody (e.g., first antibody) binds "substantially" or "at least partially" the same epitope as another antibody (e.g., second antibody) means that the epitope binding site for the first 30 antibody comprises at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more of the amino acid residues on the antigen that constitutes the epitope binding site of the second antibody. Also, that a first antibody binds substantially or partially the same or overlapping epitope as a second antibody means that the first and second antibodies compete in binding to the antigen, as described

above. Thus, the term "binds to substantially the same epitope or determinant as" a monoclonal antibody means that an antibody "competes" with the antibody.

The phrase "binds to the same or overlapping epitope or determinant as" an antibody of interest means that an antibody "competes" with said antibody of interest for at least one, (e.g., at least 2, at least 3, at least 4, at least 5) or all residues on PACAP to which said antibody of interest specifically binds. The identification of one or more antibodies that bind(s) to substantially or essentially the same epitope as the monoclonal antibodies described herein can be readily determined using alanine scanning. Additionally, any one of variety of immunological screening assays in which antibody competition can be assessed. A number of such assays are routinely practiced and well known in the art (See, e.g., U.S. Patent No. 5,660,827, issued Aug. 26, 1997, which is specifically incorporated herein by reference). It will be understood that actually determining the epitope to which an antibody described herein binds is not in any way required to identify an antibody that binds to the same or substantially the same or overlapping epitope as the monoclonal antibody described herein.

The term "Fc region" is used to define a C-terminal region of an immunoglobulin heavy chain. The "Fc region" may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. (See, Kabat et al., Sequences of Proteins of Immunological Interest, 5th edition, Bethesda, MD: U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health, 1991). The Fc region of an immunoglobulin generally comprises two constant domains, CH2 and CH3.

#### **Description of Drawings**

**Figure 1A-1G** provide the polypeptide sequences of the full-length heavy chain for antibodies Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4 (SEQ ID NOS: 401; 441; 841; 881; 921; 961; 1201; 1281; 1321; 1361; 1401; 1441; 1481; 1521; and 1561, respectively) aligned by their FRs, and CDRs, and constant regions.

**Figure 2A-2D** provide the polypeptide sequences of the full-length light chain for antibodies Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4 (SEQ ID NOS: 421; 461; 861; 901; 941; 981; 1221; 1301; 1341; 1381; 1421; 1461; 1501; 1541; and 1581, respectively) aligned by their FRs, and CDRs, and constant regions.

**Figure 3A-3S** provide the polynucleotide sequences encoding the full-length heavy chain for antibodies Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4 (SEQ ID NOS: 411; 451; 851; 891; 931; 971; 1211; 1291; 1331; 1371; 1411; 1451; 1491; 1531; and 1571, respectively) aligned by their FRs, and CDRs, and constant regions.

**Figure 4A-4J** provide the polynucleotide sequences encoding the full-length light chain Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4 (SEQ ID NOS: 431; 471; 871; 911; 951; 991; 1231; 1311; 1351; 1391; 1431; 1471; 1511; 1551; and 1591, respectively) aligned by their FRs, and CDRs, and constant regions.

**Figure 5** provides the polypeptide sequence coordinates for certain antibody heavy chain protein sequence features including the variable region and CDRs of the heavy chain for antibodies Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 6** provides the polypeptide sequence coordinates for certain antibody heavy chain protein sequence features including the constant region and framework regions FRs of the heavy chain for antibodies Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 7** provides the polypeptide sequence coordinates for certain antibody light chain protein sequence features including the variable region and CDRs of the light chain for antibodies Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 8** provides the polypeptide sequence coordinates for certain antibody light chain protein sequence features including the constant region and framework regions FRs of the light chain for antibodies Ab10, Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 9** provides the polynucleotide sequence coordinates for certain antibody heavy chain DNA sequence features including the variable region and CDRs of the heavy chain for antibodies Ab10,

Ab20, Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 10** provides the polynucleotide sequence coordinates for certain antibody heavy chain DNA sequence features including the constant region and FRs of the heavy chain for antibodies Ab10, Ab20,  
 5 Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 11** provides the polynucleotide sequence coordinates for certain antibody light chain DNA sequence features including the variable region and CDRs of the light chain for antibodies Ab10, Ab20,  
 10 Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 12** provides the polynucleotide sequence coordinates for certain antibody light chain DNA sequence features including the constant region and FRs of the light chain for antibodies Ab10, Ab20,  
 15 Ab21, Ab22, Ab23, Ab10.H, Ab21.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H2, Ab21.H3, and Ab21.H4.

**Figure 13** shows a schematic representation of the experimental setup of the experiment described in example 1. Mice were administered opioid or vehicle twice a day on days 1, 2, 3, 4, and 5; and anti-  
 20 PACAP antibody on day 3, or M65 or Olcegepant on day 5. Mechanical threshold was measured by Von Frey prior to any administration on days 1, 3, 5, and 7; and post-drug on day 5.

**Figure 14** shows the mechanical threshold measured prior to any administration (baseline) on days 1, 3, 5, and 7 for mice receiving no morphine and no treatment (VEH-VEH, positive control), mice  
 25 receiving morphine but no treatment (MORPH-VEH, negative control), and mice receiving morphine and treated with hlgG control Antibody on day 3 (M-HlgG control), anti-PACAP antibody on day 3 (M-Ab10.H), olcegepant on day 5 (M-OLCEGEPANT), or M65 on day 5 (M-M65). The data demonstrate that mice administered morphine develop opioid-induced hyperalgesia as seen by the lower mechanical threshold. Administration of anti-PACAP antibody provides long-term pain relief with  
 30 reversal to the mechanical threshold of the positive control on day 5. In contrast, no long-term pain relief was observed for mice treated with olcegepant or M65. 2-way RM ANOVA,  $p < 0.001$  time, treatment, and interaction.  $N=12$ /group (experiment was performed three times, each time with 4 mice/group). \*  $p < 0.01$  M-Ab10.H relative to MORPH-VEH.

**Figure 15** shows the mechanical threshold measured prior to any administration (Baseline) and after administration (Post-drug) of olcegepant or M65 on day 5 for mice receiving no morphine and no treatment (VEH-VEH, positive control), mice receiving morphine but no treatment (MOR-VEH, negative control), and mice receiving morphine and treated with hlgG control antibody on day 3 (M-HlgG control), anti-PACAP antibody on day 3 (M-Ab10.H), olcegepant on day 5 (M-OLCEGEPANT), or M65 on day 5 (M-M65). Subgroups M-OLCEGEPANT and M-M65 were administered the respective drug (olcegepant or M65) in between the two measurements. The data demonstrate that subgroups VEH-VEH and M-Ab10.H have a consistent high mechanical threshold at both datapoints, and that subgroups MOR-VEH and M-HlgG control have a consistent low mechanical threshold at both datapoints. Acute administration of M65 was found to provide some pain relief, whereas acute administration of Olcegepant was found to provide no significant pain relief. N=12/group (experiment was performed three times, each time with 4 mice/group).

**Figure 16** shows the mechanical threshold measured after administration (Post-drug) of olcegepant or M65 on day 5 for mice receiving no morphine and no treatment (VEH-VEH, positive control), mice receiving morphine but no treatment (MOR-VEH, negative control), and mice receiving morphine and treated with hlgG control antibody on day 3 (M-HlgG control), anti-PACAP antibody on day 3 (M-Ab10.H), olcegepant on day 5 (M-OLCEGEPANT), or M65 on day 5 (M-M65). Subgroups M-OLCEGEPANT and M-M65 were administered the respective drug (olcegepant or M65) 2 hours or 30 min prior to measurement, respectively. The data demonstrate that subgroups VEH-VEH and M-Ab10.H have a high mechanical threshold, and that subgroups MOR-VEH and M-HlgG control have a low mechanical threshold. Acute administration of M65 was found to provide some pain relief, whereas acute administration of Olcegepant was found to provide no significant pain relief. 1-way ANOVA with Holm-Sidak post-hoc analysis,  $p < 0.001$ . N=12/group (experiment was performed three times, each time with 4 mice/group). \* $p < 0.05$ , \*\*\* $p < 0.001$  relative to VEH-VEH controls. ### $p < 0.001$  relative to MORPH-VEH group.

**Figure 17** shows a schematic representation of the experimental setup of the experiment described in example 2. Mice were administered opioid or vehicle once a day on days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11; nitroglycerin (NTG) once a day on days 3, 5, 7, 9, and 11; and anti-PACAP antibody on day 10, or M65 or Olcegepant on day 12. Mechanical threshold was measured by Von Frey prior to any administration on days 1, 3, 7, 11, 12, and 14; and post-drug on day 12.

**Figure 18** shows the mechanical threshold measured prior to any administration (baseline) on days 1, 3, 7, 11, and 12 for mice receiving no morphine and no treatment (VEH-VEH, positive control), mice receiving morphine and NTG but no treatment (MOR/NTG-VEH, negative control), and mice receiving morphine and NTG and treated with hlgG control Antibody on day 10 (MOR/NTG-HlgG control), anti-PACAP antibody on day 10 (MOR/NTG-Ab10.H), olcegepant on day 12 (MOR/NTG-Olcegepant), or M65 on day 12 (MOR/NTG-M65). The data demonstrate that mice administered morphine and low dose NTG develop opioid-induced migraine-related hyperalgesia as seen by the lower mechanical threshold on days 7, 11, and 12. Administration of anti-PACAP antibody provides long-term pain relief with reversal to the mechanical threshold of the positive control on day 12. 2-way RM ANOVA,  $p < 0.001$  time, treatment, and  $p < 0.01$  interaction.  $N = 8(7)/\text{group}$  (experiment was performed twice, each time with 4(3) mice/group). \*\*  $p < 0.01$  Mor/NTG-Ab10.H relative to MOR/NTG-VEH.

**Figure 19** shows the mechanical threshold measured prior to any administration (Baseline) and after administration (Post-drug) of olcegepant or M65 on day 12 for mice receiving no morphine, NTG, and no treatment (VEH-VEH, positive control), mice receiving morphine and NTG but no treatment (MOR-VEH, negative control), and mice receiving morphine and NTG and treated with hlgG control antibody on day 10 (MOR/NTG-HlgG control), anti-PACAP antibody on day 10 (MOR/NTG-Ab10.H), olcegepant on day 12 (MOR/NTG-Olcegepant), or M65 on day 12 (MOR/NTG-M65). Subgroups MOR/NTG-Olcegepant and MOR/NTG-M65 were administered the respective drug (olcegepant or M65) in between the two measurements. The data demonstrate that subgroups VEH-VEH and MOR/NTG-Ab10.H have a consistent high mechanical threshold at both datapoints, and that subgroups MOR/NTG-VEH and MOT/NTG-HlgG control have a consistent low mechanical threshold at both datapoints. Acute administration of M65 was found to provide some pain relief, whereas acute administration of Olcegepant was found to provide no significant pain relief.  $N = 8(7)/\text{group}$  (experiment was performed twice, each time with 4(3) mice/group).

**Figure 20** shows the mechanical threshold measured after administration (Post-drug) of olcegepant or M65 on day 12 for mice receiving no morphine and NTG, and no treatment (VEH-VEH, positive control), mice receiving morphine and NTG but no treatment (MOR/NTG-VEH, negative control), and mice receiving morphine and NTG and treated with hlgG control antibody on day 10 (MOR/NTG-HlgG control), anti-PACAP antibody on day 10 (MOR/NTG-Ab10.H), olcegepant on day 12 (MOR/NTG-Olcegepant), or M65 on day 12 (MOR/NTG-M65). Subgroups MOR/NTG-Olcegepant and MOR/NTG-M65 were administered the respective drug (olcegepant or M65) 2 hours or 30 min prior to measurement, respectively. The data demonstrate that subgroups VEH-VEH and MOR/NTG-Ab10.H

have a high mechanical threshold, and that subgroups MOR/NTG-VEH and MOR/NTG-HlgG control have a low mechanical threshold. Acute administration of M65 was found to provide some pain relief, whereas acute administration of Olcegepant was found to provide no significant pain relief. 1-way ANOVA with Holm-Sidak post-hoc analysis,  $p < 0.001$ .  $N = 8(7)/\text{group}$  (experiment was performed twice, each time with 4(3) mice/group). \*\*\* $p < 0.001$  relative to VEH-VEH controls, ### $p < 0.001$  relative to MOR/NTG-VEH group.

**Figure 21** shows the mechanical threshold measured prior to any administration (Baseline) and after administration (Post-drug) of olcegepant or M65 on day 12 for mice receiving no morphine, NTG, and no treatment (VEH-VEH, positive control), mice receiving morphine and NTG but no treatment (MOR-VEH, negative control), and mice receiving morphine and NTG and treated with hlgG control antibody on day 10 (MOR/NTG-HlgG control), anti-PACAP antibody on day 10 (MOR/NTG-Ab10.H), olcegepant on day 12 (MOR/NTG-Olcegepant), or M65 on day 12 (MOR/NTG-M65). Subgroups MOR/NTG-Olcegepant and MOR/NTG-M65 were administered the respective drug (olcegepant or M65) in between the two measurements. The data demonstrate that subgroups VEH-VEH and MOR/NTG-Ab10.H have a consistent high mechanical threshold at both datapoints, and that subgroups MOR/NTG-VEH and MOR/NTG-HlgG control have a consistent low mechanical threshold at both datapoints. Acute administration of M65 was found to provide some pain relief, whereas acute administration of Olcegepant was found to provide no significant pain relief.  $N = 8(7)/\text{group}$  (experiment was performed twice, each time with 4(3) mice/group).

**Figure 22** shows that 20 mg/kg PACAP antibody attenuate the development of cephalic allodynia in the OIH model. Mice were tested on day 6 after post injection. 1-way ANOVA with Holm-Sidak post-hoc analysis \*\* $p < 0.01$  compared to VEH-VEH,  $p < 0.05$  compared to MORPH-VEH. The mice were also tested on days 1, 2 and 5 and the results showed that the mice treated with PACAP antibody had a reduction already at day 2, and at day 5 and 6 the difference to VEH-VEH was significant.

**Figure 23** shows that 20 mg/kg of Ab 10.H prevented the development of cephalic allodynia associated with opioid exacerbated migraine. Cephalic mechanical baseline taken on naïve mice before morphine (mor) injection (day 1), on day 3 before fits NTG injection, on day 7 before Morphine/NTG injection, and on day 12, 20-22 hours after last Morphine/NTG injection and on day 14 before collection of blood and tissue. The top curves in the diagram separating after day 3, shows the curves for the veh/veh group (non-filled circles) and the Mor/NTG-Ab 10.H PACAP antibody (filled circle). The bottom curves shows, Mor/NTG-CTNL, Mor/NTG-Olcegepant, Mor/NTG-Vhl, and Mor/NTG-M65.



2-way ANOVA factors of treatment and time  $p < 0.001$  treatment, time and interaction. In day 7 to day 14 Ab 10H is significant different from Morphine/NTG-Veh or Morphine/Veh-CNTL ab

**Figure 24** shows that pre-treatment with the PACAP antibody Ab 10.H (20 mg/kg for both) prevented the development of cephalic allodynia. Analysis on day 12. 1-way ANOVA with Holm-Sidak post-hoc analysis  $**p < 0.01$  compared to VEH-VEH,  $p < 0.05$  compared to MORPH-VEH.

#### Detailed Description of the Invention

The present invention relates to a method of treatment and/or preventing of opioid-induced pain, such as opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA) by administration of an antibody and/or antigen-binding fragment thereof to a subject in need thereof, wherein such antibody and/or antigen-binding fragment thereof specifically bind to Pituitary Adenylate Cyclase-Activating Polypeptide ("PACAP").

In one embodiment, the present invention relates to a method of treatment and/or preventing of pain by administration of an anti-PACAP antibody and/or antigen-binding fragment thereof to a subject in need thereof.

In one embodiment, the pain is selected from the group consisting of neuropathic pain, nociceptive pain, inflammatory pain, mixed pain, and visceral pain. In one embodiment, the pain is neuropathic pain, such as central neuropathic pain and/or peripheral neuropathic pain. In one embodiment, the pain is worsening of neuropathic pain resulting from exposure of said subject to opioids. In one embodiment, the pain is hyperalgesia and/or allodynia. In one embodiment, the pain is hyperalgesia and/or allodynia resulting from exposure of the subject to opioids, such as opioid-induced hyperalgesia and/or opioid-induced allodynia. In one embodiment, the pain is migraine resulting from exposure of the subject to opioids, such as opioid-induced chronic migraine.

#### Opioid-induced Pain

Opioid analgesics are an often-prescribed medication class, and their use has increased dramatically, with the number of prescriptions doubling between 1998 and 2010. Moreover, long-term use of opioids is becoming more prevalent. Opioid-induced pain is a common problem to patients administered opioids for the treatment of pain. In one embodiment, the present invention relates to treatment of opioid-induced pain, such as treatment of opioid-induced chronic migraine, OIH, and/or

OIA. In a preferred embodiment, the opioid-induced pain is opioid-induced chronic migraine or opioid-induced hyperalgesia, such as opioid-induced hyperalgesia.

5 The term opioid as used herein refer to substances, both natural occurring opiates and synthetic or semi-synthetic opioids, which bind to the opioid receptors. The term opioids and opiates may be used herein interchangeably. Opioids are potent analgesics widely used in clinical practice. Opiates refer to naturally occurring alkaloids extracted from poppy pods (Opium Poppy; *Papaver somniferum*). Semi-synthetic opioids are synthesized from naturally occurring opiates as starting material, and include heroin (diamorphine), oxycodone, hydrocodone, dihydrocodeine, hydromorphone, oxymorphone, 10 buprenorphine and etorphine. Synthetic opioids are synthesized compounds that bind to opioid receptors, and include methadone, pethidine, fentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, tramadol, tapentadol and loperamide.

15 In one embodiment, the opioid is an opioid analgesics, such as an opioid analgesics selected from the group consisting of codeine, dihydrocodeine, morphine or a morphine derivative or pharmaceutically acceptable salt thereof, codeine, dihydrocodeine, oxycodone, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanil, meperidine, methadone, nalbuphine, propoxyphene, and pentazocine, or pharmaceutically acceptable salts thereof.

20 In one embodiment, the pain is resulting from the subject being administered an opioid, such as being administered an opioid as an analgesic for the treatment of an original pain. Thus, in one embodiment, the pain is opioid-induced pain. In one embodiment, the pain is resulting from the subject being administered an opioid for treatment of acute pain, such as for the treatment of pain associated with 25 cancer, pain associated with surgery, and/or pain resulting from neurodegenerative conditions, such as rheumatoid arthritis. Thus, in one embodiment, the original pain treated with an opioid is acute pain, such as for the treatment of pain associated with cancer, pain associated with surgery, and/or pain resulting from neurodegenerative conditions, such as rheumatoid arthritis.

30 In one embodiment, the pain is resulting from the subject being administered an opioid for treatment of chronic pain, such as for the treatment of headaches, back pain, migraine, neuropathic pain, and/or fibromyalgia. Thus, in one embodiment, the original pain treated with an opioid is chronic pain, such as for the treatment of headaches, back pain, migraine, neuropathic pain, and/or fibromyalgia.

Further exemplary original pain associated diseases or conditions for which an opioid may be administered, include but are not limited to, general pain, chronic pain, inflammatory pain, post-operative incision pain, post-surgical pain, trauma-related pain, lower back pain, eye pain, tooth pain, complex regional pain syndrome, cancer pain (e.g., primary or metastatic bone cancer pain), fracture pain, osteoporotic fracture pain, pain resulting from burn, gout joint pain, pain associated with sickle cell crises, pain associated with temporomandibular disorders, cirrhosis, hepatitis, neurogenic pain, neuropathic pain, nociceptive pain, visceral pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, and dyspepsia.

In one embodiment, the original pain is headache and/or migraine. Thus, in one embodiment, the subject is administered an opioid for the treatment of headache and/or migraine, such as headache and/or migraine selected from migraine with or without aura, hemiplegic migraine, cluster headache, migrainous neuralgia, chronic headache, and tension headache. In one embodiment, the subject is administered an opioid for treatment of migraine. Administration of opioids to a subject for the treatment of migraine may result in the development of chronic migraine. Routine use of opioids for the treatment of migraine often leads to more frequent and severe headaches. Prolonged use of opioids for the treatment of migraine may trigger a transition from episodic migraine to chronic migraine, and often the damage cannot be undone by subsequent detoxification from opioid dependency. Chronic migraine is defined as a type of chronic daily headache (CDH, headaches on 15 or more days per month of at least 3 months), wherein at least eight headache days per month meet the criteria for migraine without aura or responding to migraine specific treatment. Thus, in one embodiment, the opioid-induced pain is opioid-induced chronic migraine. In one embodiment, the opioid-induced chronic migraine results from administration of an opioid for treatment of pain, such as headache and/or migraine, resulting in opioid-induced exacerbated migraine, such as migraine resulting from exposure to low doses of a migraine trigger which would usually not result in migraine, however, due to the opioid-treatment, the migraine response is exacerbated resulting in an increase in the number of days with migraine and development of chronic migraine.

Administration of an opioid to a subject may also result in the development of opioid-induced hyperalgesia. Opioid-induced hyperalgesia (OIH) (also called opioid-induced abnormal pain sensitivity) is defined as a state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of an

original pain becomes more sensitive to certain painful stimuli. Thus, in one embodiment, the opioid-induced pain is opioid-induced hyperalgesia.

5 The type of pain experienced in OIH may be the same as the original pain initially treated by administration of an opioid or may be different from the original pain. In one embodiment, the OIH is characterized by

- a) diffuse pain,
- b) pain which is less defined in quality,
- c) pain which quality is harder to define,
- 10 d) original pain which affects a broader area than was originally affected,
- e) increased pain intensity without the underlying medical condition for the original pain having been worsened,
- f) pain which extends to other areas of distribution from the original pain, and/or
- g) pain which is different from the original pain and which has developed without a specific
- 15 diagnosis.

In one embodiment, the pain in OIH result from one or more of the following:

- a) pain in the absence of a noxious stimulus (spontaneous pain),
- b) increased duration of pain in response to brief stimulation (ongoing pain or hyperpathia),
- 20 c) reduced pain threshold (allodynia),
- d) increased responsiveness to suprathreshold stimulation (hyperalgesia),
- e) spread of pain and hyperalgesia to uninjured tissue (referred pain and secondary hyperalgesia), and/or
- f) abnormal sensations (e.g., dysesthesia, paresthesia).

25

In one embodiment, the OIH is a result of the subject having been administered high doses of opioids and/or having been administered opioids for a longer period of time. Alternatively, the OIH may occur after a single dose of opioids or after only a few doses of opioids. Thus, in one embodiment, the OIH occurs after acute opioid administration or after chronic opioid administration.

30

Administration of an opioid to a subject may alternatively or in addition to OIH result in the development of opioid-induced allodynia (OIA), wherein a patient receiving opioids for the treatment of an original pain is experiencing pain from stimulations which were not painful before, such as for example wherein stroking the skin with a cotton ball produces a painful reaction. Thus, in one

embodiment, the opioid-induced pain is opioid-induced hyperalgesia and/or opioid-induced allodynia.  
In one embodiment, the opioid-induced pain is opioid-induced allodynia.

#### **Method of Treatment of Pain**

5 In one embodiment, the present invention provides a method for ameliorating, reducing the symptoms of, treating and/or preventing pain, such as hyperalgesia or allodynia.

In one embodiment, the present invention provides a method for ameliorating pain, such as hyperalgesia or allodynia, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as described herein.

10 In one embodiment, the present invention provides a method for reducing the symptoms of pain, such as hyperalgesia or allodynia, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as described herein.

In one embodiment, the present invention provides a method for treating pain, such as hyperalgesia  
15 or allodynia, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as described herein.

In one embodiment, the present invention provides a method for preventing pain, such as hyperalgesia or allodynia, said method comprising administering to a subject in need thereof an anti-  
20 PACAP antibody and/or antigen-binding fragment thereof as described herein.

In one embodiment, the present invention provides a method for ameliorating, reducing the symptoms of, treating, and/or preventing opioid-induced pain, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as  
25 described herein.

In one embodiment, the present invention provides a method for ameliorating opioid-induced pain, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as described herein.  
30

In one embodiment, the present invention provides a method for reducing the symptoms of opioid-induced pain, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as described herein.

In one embodiment, the present invention provides a method for treating opioid-induced pain, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as described herein.

5 In one embodiment, the present invention provides a method for preventing opioid-induced pain, said method comprising administering to a subject in need thereof an anti-PACAP antibody and/or antigen-binding fragment thereof as described herein.

The present invention further includes the use of an anti-PACAP antibody and/or antigen-binding fragment thereof as disclosed herein in the manufacture of a medicament for the ameliorating,  
10 reducing the symptoms of, treating, and/or preventing of opioid-induced pain, such as opioid-induced chronic migraine, OIH and/or OIA.

The present invention further includes an anti-PACAP antibody and/or antigen-binding fragment thereof as disclosed herein for use in the ameliorating, reducing the symptoms of, treating, and/or  
15 preventing of opioid-induced pain, such as opioid-induced chronic migraine, OIH and/or OIA.

In one embodiment, the method of the present disclosure prevents opioid-induced pain. The opioid-induced pain may be prevented by prophylactically administering an anti-PACAP antibody and/or antigen-binding fragment thereof to a subject who is about to receive an opioid treatment, such as to  
20 a subject who is about to receive an opioid treatment and who is considered at risk of developing opioid-induced pain, for example, wherein the subject has a prior or family history of opioid-induced pain. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is administered prior to the administration of an opioid. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is administered about one week or 2 weeks prior to, or 6, 5,  
25 4, 3, 2 or 1 day prior to, or 20, 16, 12, 8, 6, 4, 2 or 1 hour prior to the administration of an opioid.

In one embodiment, the opioid and the anti-PACAP antibody and/or antigen-binding fragment thereof are co-administered to provide pain relief of the original pain while preventing opioid-induced pain.  
In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is  
30 administered concurrent to the administration of an opioid.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is administered after the administration of an opioid. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is administered within about 1 hour, 6 hours, 12 hours, 1

day, 2 days, 4 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 8 months, 10 months or 1 year after the administration of an opioid.

When a subject suffers from opioid-induced pain, one currently applied treatment is to gradually  
5 reduce the opioid treatment regimen and possibly to completely stop the opioid treatment. Such  
reduction or stop of opioid treatment may result in relief from the opioid-induced pain, however, also  
may leave the original pain untreated, resulting in suboptimal pain alleviation for the patient. The  
present invention provides a method for ameliorating, reducing the symptoms of and/or treating  
10 opioid-induced pain, said method comprising administering to a subject in need thereof an anti-PACAP  
antibody and/or antigen-binding fragment thereof as described herein. In one embodiment, the  
opioid treatment regimen is gradually reduced or completely stopped prior to or simultaneous with  
administration of the anti-PACAP antibody and/or antigen-binding fragment thereof. In a separate  
embodiment, the opioid treatment is continued while the subject is additionally being treated with an  
anti-PACAP antibody and/or antigen-binding fragment thereof. In such embodiment, the pain relief  
15 for the treated subject is optimal resulting from the continued opioid administration for treatment of  
the original pain, while the opioid-induced pain is ameliorated, the symptoms are reduced, and/or  
treated by administration of an anti-PACAP antibody and/or antigen-binding fragment thereof. In one  
embodiment, the opioid and the anti-PACAP antibody and/or antigen-binding fragment thereof are  
co-administered to provide pain relief of the original pain while ameliorating, reducing the symptoms  
20 of, and/or treating the opioid-induced pain. In one embodiment, the method as herein described  
includes the administration of an anti-PACAP antibody and/or antigen-binding fragment and an  
opioid, and which combined administration elicits an additive or synergistic effect on ameliorating  
and/or preventing pain, such as hyperalgesia, allodynia or opioid-induced pain, optionally opioid-  
induced pain, optionally opioid-induced pain selected from the group consisting of opioid-induced  
25 chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

In one embodiment, the opioid-induced pain is unsuccessfully attempted treated by reducing the  
opioid treatment regimen or by completely stopping the opioid treatment, whereby the opioid-  
induced pain is present in the subject despite of the reduction in or stopping of the opioid treatment.  
30 The opioid-induced pain in such embodiment may be treated by administration of an anti-PACAP  
antibody and/or antigen-binding fragment thereof to said subject. Thus, in one embodiment the anti-  
PACAP antibody and/or antigen-binding fragment thereof is administered to a subject who has  
developed opioid-induced pain and is no longer being administered an opioid.

**Method of Treatment of Medication Overuse Headache**

The present disclosure also provides methods of treating or preventing medication overuse headache, e.g., associated with the overuse of anti-migraine drugs and/or associated with triptan and/or ergot and/or analgesic overuse, comprising administering to a patient in need an effective amount of the

5    PACAP antibodies of the invention. Said medication overuse headache may be determined based on meeting the following criteria: (a) headache occurring on 15 or more days/month in a patient with a pre-existing headache disorder; and (b) overuse for more than 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.

10    Said overuse may comprise use of an ergot alkaloid (e.g., ergotamine) on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month,

15    or use of a combination of two or more drug classes (as further described below) on 10 or more days/month.

In the methods herein, said triptan may include, without limitation thereto, any one of or any combination of triptans such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan,

20    almotriptan, and frovatriptan, among others.

Said medication overuse headache may comprise ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not

25    individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

Said non-opioid analgesic-overuse headache may comprise paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic

30    acid (aspirin)-overuse headache or ibuprofen-overuse headache, or another non-opioid analgesic-overuse headache.



Said ergotamine-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of an ergot alkaloid such as ergotamine on 10 or more days/month for more than 3 months.

- 5 In the methods herein, said ergot alkaloid may comprise ergotamine, nicergoline, methysergide, or dihydroergotamine.

- Said triptan-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one  
10 or more triptans on 10 or more days/month for more than 3 months.

- Said non-opioid analgesic-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more non-opioid analgesics (such as paracetamol (acetaminophen),  
15 acetylsalicylic acid (aspirin), ibuprofen, another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

In the methods herein, said NSAID may comprise any NSAID or combination thereof, including without limitation thereto, ibuprofen, naproxen, or indomethacin.

- 20 Said combination-analgesic-overuse headache may comprise headache occurring on 15 or more days/month developing as a consequence of regular use of one or more combination-analgesics on 10 or more days/month for more than 3 months. In the context of medication overuse headache, the term combination-analgesic refers to formulations combining drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or analgesics in combination with  
25 agents acting as adjuvants (for example, caffeine). Commonly overused combination-analgesics combine non-opioid analgesics with at least one opioid, barbiturate such as butalbital and/or caffeine. In exemplary embodiments, the combination-analgesic overuse-headache is due to the combination of acetaminophen, aspirin, and caffeine, e.g., EXCEDRIN<sup>®</sup> or EXCEDRIN MIGRAINE<sup>®</sup>.
- 30 Other known combination analgesics comprise an analgesic in combination with at least one non-analgesic, e.g., with a vasoconstrictor drug such as pseudoephedrine for sinus-related preparations, antihistamine drug used to treat allergy sufferers, etc.

Said opioid-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more opioids 10 or more days/month for more than 3 months.

- 5 Said medication-overuse headache attributed to multiple drug classes not individually overused may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of any combination of ergotamine, triptans, non-opioid analgesics and/or opioids on a total of at least 10 days/month for more than 3 months without overuse of any single drug or drug class alone.

10

In the methods herein, said opioid may be any one or any combination of opioid drugs, including without limitation thereto, oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, thebaine, oripavine, mixed opium alkaloids such as papaveretum, diacetylmorphine, nicomorphine, dipropanoylmorphine, diacetyldihydromorphine, acetylpropionylmorphine, desomorphine,

- 15 methyldesorphine, dibenzoylmorphine, ethylmorphine, heterocodeine, buprenorphine, etorphine, hydromorphone, oxymorphone, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, ohmefentanyl, pethidine (meperidine), ketobemidone, Desmethyprodine or 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), allylprodine, prodine, 4-Piperidinol or 1-phenethyl-4-phenyl acetate (PEPAP), Trimeperidine (Promedol), diphenylpropylamine, propoxyphene, 20 dextropropoxyphene, dextromoramide, bezitramide, piritramide, among others.

Said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of any combination of ergotamine, triptans, non-opioid analgesics and/or opioids on at least 10 days/month for more than 3 months, 25 wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

- Said medication-overuse headache attributed to other medication may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and 30 developing as a result of regular intake of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

#### Administration and Doses

The method of the present disclosure may comprise administering the anti-PACAP antibody, or antigen-binding fragment thereof in a therapeutically effective amount to the subject in need thereof. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is administered in the form of a pharmaceutical composition. In one embodiment, the anti-PACAP  
5 antibody and/or antigen-binding fragment thereof, as well as combinations of the antibodies and/or antigen-binding fragments thereof herein disclosed, are administered to a subject in a pharmaceutical formulation.

A "pharmaceutical composition" or "medicament" refers to a chemical or biological composition  
10 suitable for administration to a subject, preferably a mammal, more preferably a human. 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,  
15 subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is administered to a subject at a concentration of between 0.1 mg/ml and about any one of 0.5, 1, 5, 10,  
20 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 mg/ml, +/-10% error.

In another embodiment of the invention, the anti-PACAP antibody and/or antigen-binding fragment thereof is administered to a subject at a dose of between about 0.01 and 100.0 or 200.0 mg/kg of  
25 body weight of the recipient subject. In certain embodiments, depending on the type and severity of the opioid-induced pain, about 1 µg/kg to 50 mg/kg (e.g., 0.1-20 mg/kg) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. In another embodiment, about 1 µg/kg to 15 mg/kg (e.g., 0.1 mg/kg-10 mg/kg) of antibody is an initial candidate dosage for administration to the patient. A  
30 typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on several factors, e.g., the particular mammal being treated, the clinical condition of the individual patient, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. However, other dosage regimens may be useful.

For example, in addition to the relative dosages (mg/kg) discussed herein, the subject anti-PACAP antibody and/or antigen-binding fragment thereof can be administered to a subject at an absolute dose (mg). Accordingly, in one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof described herein is administered to a subject at a dose of between about 1  
5 microgram and about 1000 milligrams regardless of the route of administration.

In a preferred embodiment of the invention, the anti-PACAP antibodies described herein, or antigen-binding fragments thereof, as well as combinations of said antibodies or antigen-binding fragments thereof, are administered to a recipient subject with a frequency of once every twenty-six weeks or  
10 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.

According to preferred embodiments, the antibody containing medicament or pharmaceutical composition is peripherally administered to a subject via a route selected from one or more of: orally,  
15 sublingually, buccally, topically, rectally, via inhalation, transdermally, subcutaneously, intravenously, intra-arterially, or intramuscularly, via intracardiac administration, intraosseously, intradermally, intraperitoneally, transmucosally, vaginally, intravitreally, epicutaneously, intra-articularly, peri-articularly, or locally.

## 20 **Subject**

The subject to which the anti-PACAP antibody and/or antigen-binding fragment thereof is administered may be, e.g., any human or non-human animal that is in need of such treatment, prevention and/or amelioration. For example, the subject can be an individual that is diagnosed with opioid-induced pain, such as opioid-induced chronic migraine, OIH and/or OIA. In one embodiment,  
25 the subject is a subject not experiencing adequate pain relief from opioid treatment. In one embodiment, the subject is a subject experiencing increased pain after being subjected to opioid treatment. In one embodiment, the subject is a migraineur who did not adequately respond to opioid treatment, such as a migraineur experiencing increased migraine pain and/or increased frequency of days of migraine. In one embodiment, the subject is about to receive an opioid treatment, such as a  
30 subject who is about to receive an opioid treatment and who is considered at risk at developing opioid-induced pain, for example wherein the subject has a prior or family history of opioid-induced pain. In a preferred embodiment, the subject is a human. In one embodiment the subject has previously received an opioid and has developed opioid-induced pain, such as a subject who suffers from opioid-induced pain but is no longer being administered an opioid.

**PACAP**

PACAP is a multifunctional vasodilatory peptide with expression throughout the central nervous system ("CNS") and periphery. PACAP is a member of the secretin/VIP/GRH family. PACAP exists in two  $\alpha$ -amidated active forms, PACAP38 (SEQ ID NO: 1241) and PACAP27 (SEQ ID NO: 1242). Herein, the term "PACAP" includes either or both of PACAP38 and PACAP27 unless expressly indicated otherwise. PACAP is highly conserved between species.

In humans, PACAP is derived from a 176 amino acid precursor protein (preproPACAP) and the gene is located on chromosome 18p11, with PACAP38 encoded for by exon 5. (See, Vaudry et al., *Pharmacol. Rev.*, 61:283-357, 2009). PreproPACAP contains an N-terminal 24 amino acid signal protein, a 29 amino acid PACAP-related peptide and PACAP in the C-terminal domain. The precursor is metabolized by prohormone convertase enzymes into biologically active PACAP38 and PACAP27.

VIP (SEQ ID NO: 1243) belongs to the same protein family as PACAP and shares high homology with PACAP, i.e., VIP and PACAP27 have 68% sequence homology at the amino acid level, as well as similar overall secondary structure, i.e. long alpha-helical structures at the C-terminus.

PACAP's actions are mediated via three different G-protein coupled receptors: PAC1-R, VPAC1-R, and VPAC2-R. VPAC1-R can associate with all of the receptor-associated membrane proteins ("RAMPs," See Kaiser and Russo, *Neuropeptides* 47:451-461, 2013). PAC1-R is selective for PACAP, whereas VPAC1-R and VPAC2-R bind to both VIP and PACAP with high affinity. PAC1-R binds to PACAP with 100-1000-fold higher affinity than VIP, i.e.,  $K_D \sim 0.5$  nM for PACAP27/PACAP38 vs.  $K_D \sim 500$  nM for VIP. Conversely, VPAC1-R and VPAC2-R have equal affinities for PACAP and VIP ( $K_D \sim 1$  nM). (See, Schytz et al., 2010). All three receptors are widely expressed in both peripheral tissues and in the CNS, with PAC1-R predominantly expressed in the CNS, most abundantly in the olfactory bulb, thalamus, hypothalamus, the dentate gyrus of the hippocampus and in granule cells of the cerebellum. (See, Hashimoto et al., *J. Comp. Neurol.*, 371:567-577, 1996; and Shioda et al., *Neurosci. Res.*, 28:345-354, 1997).

Activation of the PAC1-R, VPAC1-R, and/or VPAC2-R results in increased adenylate cyclase activity and, thus, increased cAMP production. However, PACAP receptors can also mediate their effects through PLC, leading to increased  $Ca^{2+}$  levels, and PLD.

PACAP has a wide range of biological effects, including a role in neurodevelopment, neuroprotection, neuromodulation, neurogenic inflammation, and nociception. PACAP is also reported to interact with glycosaminoglycans ("GAGs"). GAGs are long, unbranched polysaccharides composed of repeating disaccharide units, such as heparin, chondroitin, keratin, and hyaluronic acid. It has been shown that the cellular uptake of PACAP is dependent on the expression of GAG proteins and that PACAP bound to sulfated GAGs. Particularly, it was determined that PACAP38 binding to GAGs was capable of inducing receptor-independent cellular uptake of PACAP38. This study further demonstrated that a random coil-to- $\alpha$ -helix transition in PACAP38 was essential for GAG-dependent uptake of PACAP38, as a mutant PACAP38 that could not undergo the structural transition was not internalized by GAG-containing cell lines as efficiently as the wild-type form of PACAP38 (Neree et al., *FEBS Lett.*, 588(24):4590-4596, 2014). In a follow up study, it was determined that PACAP's ability to cluster GAGs, i.e., heparin, was directly related to its ability to function as a cell penetrating peptide ("CPP"). It is hypothesized that this activity is attributable to the heparin-binding, or Cardin-Weintraub, motif found in secretin/glucagon/GHRH family members, such as PACAP (Neree et al., *Int. J. Mol. Sci.*, 16:27391-27400, 2015). Interestingly, Neree et al. (2015) presented data demonstrating that PACAP38 was able to cluster sulfated GAGs *in vitro*. These data suggested that the observed clustering effect is important for the GAG-mediated cellular uptake of PACAP38, as other peptides, such as glucagon, displayed higher binding affinities for sulfated GAGs (heparin) but are not internalized by cells as efficiently as PACAP38. Further, it is reported that in *in vitro* studies in which cells are exposed to PACAP, cartilage formation is increased, including cartilage matrix that is rich in sulphated GAG proteins, consistent with its putative protective role expressed during various cellular stress responses (Juhász et al., *PLoS ONE*, 9(3):e91541, 2014). Using cell types that lack PACAP-specific receptors on their plasma membranes, such as CHO-K1 cells, Doan et al. presented data demonstrating the ability of such cells to engage in receptor-independent cellular uptake of various forms of fluorescently labeled PACAP38 and PACAP27 (Doan et al., *Biochem. Biophys. Acta*, 1823:940-949, 2012).

#### **Anti-PACAP Antibodies and Antigen-binding Fragments Thereof Having Binding Activity for PACAP**

The present invention provides a method for treatment and/or prevention of opioid-induced pain, such as opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA) by administration of an antibody or antigen-binding fragment thereof which binds PACAP, including human PACAP.

Antibodies or antigen-binding fragments thereof which binds PACAP (anti-PACAP antibodies and antigen-binding fragments thereof), including those having different CDRs, and epitopic specificity may be obtained using methods that are generally known in the art. Such antibodies and/or antigen-binding fragments thereof antagonize the biological effects of PACAP *in vivo* and therefore are useful

5 in treating or preventing PACAP-related conditions including opioid-induced pain, such as opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

In some embodiments, an anti-PACAP antibody and/or antigen-binding fragment thereof according to the invention will interfere with, block, reduce, or modulate the interaction between PACAP and its

10 receptor(s) (e.g., PAC1-R, VPAC1-R, and VPAC2-R). In some embodiments, an anti-PACAP antibody and/or antigen-binding fragment thereof according to the invention is “neutralizing”, e.g., it totally prevents the specific interaction of PACAP with PAC1-R, VPAC1-R, and/or VPAC2-R. In some embodiments, the antibody or antigen-binding fragment thereof neutralizes PACAP, e.g., by remaining bound to PACAP in a location and/or manner that prevents PACAP from specifically binding to PAC1-

15 R, VPAC1-R, and/or VPAC2-R. As used herein, the term “one or more biological effects associated with PACAP” refers to any biological effect mediated, induced, or otherwise attributable to PACAP, e.g., binding properties, functional properties, and other properties of biological significance. Non-limiting exemplary biological effects of PACAP include PACAP binding to PAC1-R, VPAC1-R, and/or VPAC2-R; PACAP activating PAC1-R, VPAC1-R, and/or VPAC2-R-mediated signaling; PACAP-mediated increase in

20 cAMP production; PACAP-mediated increase in PLC activity; PACAP-mediated increase in PLD activity; PACAP-mediated increase in  $Ca^{2+}$  levels; and PACAP-mediated vasodilation, photophobia, mast cell degranulation, and/or neuronal activation. The subject anti-PACAP antibody and/or antigen-binding fragment thereof is capable of inhibiting one, a combination of, or all of these exemplary PACAP biological activities.

25 The anti-PACAP antibody and/or and antigen-binding fragment thereof of the present disclosure are preferably a human, humanized, or chimerized anti-PACAP antibody and/or antigen-binding fragment thereof, that antagonize, inhibit, neutralize, or block at least one biological effect associated with human PACAP. In certain embodiments, the anti-PACAP antibody and/or antigen-binding fragment

30 thereof inhibit or neutralize at least one biological effect elicited by PACAP, which includes PACAP27 and/or PACAP38, as discussed infra. In other embodiments, the anti-PACAP antibody and/or antigen-binding fragment thereof neutralize or inhibit PACAP activation of at least one of PAC1-R, VPAC1-R, and/or VPAC2-R; neutralize or inhibit PACAP activation of each of PAC1-R, VPAC1-R, and VPAC2-R; and/or neutralize or inhibit PACAP activation of PAC1-R; and/or inhibits PACAP binding to the cell

surface, e.g., via a glycosaminoglycan ("GAG") inhibit PACAP-induced cAMP production; and/or when administered to a subject reduce PACAP-induced vasodilation, photophobia, mast cell degranulation, and/or neuronal activation. In yet other embodiments, the anti-PACAP antibody and/or antigen-binding fragment thereof is capable of inhibiting PACAP binding to at least one of PAC1-R, VPAC1-R, and/or VPAC2-R; are capable of inhibiting PACAP binding to each of PAC1-R, VPAC1-R, and/or VPAC2-R; or are capable of inhibiting PACAP binding to PAC1-R. In other embodiments, the anti-PACAP antibody and/or antigen-binding fragment thereof inhibits PACAP-induced cAMP production. In some embodiments, the antibody or antigen-binding fragment thereof according to the invention is capable of inhibiting PACAP-mediated activity (including binding to PAC1R-expressing cells). In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof employed in the methods binds to PACAP27 and/or PACAP38 and blocks PACAP27 and/or PACAP38 binding to PAC1-R, VPAC1-R, and/or VPAC2-R. In another embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof employed in the methods binds to PACAP27 and/or PACAP38 and blocks PACAP27 and/or PACAP38 binding to each of PAC1-R, VPAC1-R, and VPAC2-R. Preferably, the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP27 and/or PACAP38 and blocks PACAP27 and/or PACAP38 binding to PAC1-R.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprise one or more of the following: (a) inhibits or neutralizes at least one biological effect elicited by PACAP; (b) neutralizes or inhibits PACAP activation of at least one of PAC1 receptor ("PAC1-R"), vasoactive intestinal peptide receptor type 1 ("VPAC1-R"), and/or vasoactive intestinal peptide receptor type 2 ("VPAC2-R"); (c) neutralizes or inhibits PACAP activation of each of PAC1-R, VPAC1-R, and VPAC2-R; (d) neutralizes or inhibits PACAP activation of PAC1-R; (e) is capable of inhibiting PACAP binding to at least one of PAC1-R, VPAC1-R, and/or VPAC2-R; (f) is capable of inhibiting PACAP binding to each of PAC1-R, VPAC1-R, and/or VPAC2-R; (g) is capable of inhibiting PACAP binding to PAC1-R-expressing cells; (h) is capable of inhibiting PACAP binding to the cell surface, e.g., via a glycosaminoglycan ("GAG"); (i) does not inhibit PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG; (j) inhibits PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG; (k) inhibits PACAP-induced cAMP production; and/or (l) when administered to a subject reduces PACAP-induced vasodilation, photophobia, mast cell degranulation and/or neuronal activation.

In yet other embodiments, the anti-PACAP antibody and/or antigen-binding fragment thereof, alone or in combination, when administered to a subject, e.g., a human, reduces PACAP-induced vasodilation, photophobia, mast cell degranulation, and/or neuronal activation. In related



embodiments, the human or humanized anti-PACAP antibody and/or antigen-binding fragment thereof is suitable for treating a human subject having an acute, episodic or chronic condition associated with increased vasodilation, photophobia, mast cell degranulation, and/or neuronal activation.

5

In a preferred embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof does not substantially interact with (bind to) VIP. The anti-PACAP antibody and/or antigen-binding fragment thereof comprising the invention has binding affinity for PACAP, wherein the binding affinity comprises the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binding to PACAP38 and PACAP27, but not binding VIP, and/or antibodies or antigen-binding fragment thereof specifically binding to PACAP38, but not binding to PACAP27 or VIP, and/or antibody and/or antigen-binding fragment thereof specifically binding to a linear and/or conformational epitope within PACAP38 and/or PACAP27. Preferably, the anti-PACAP antibody and/or antigen-binding fragment thereof has no cross-reactivity or minimal cross-reactivity with VIP.

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The antibodies of the present invention also include humanized and chimeric forms of antibodies of the present disclosure. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is chimeric, human or humanized. The chimeric and humanized antibodies may include an Fc derived from IgG1, IgG2, IgG3, or IgG4 constant regions. In one embodiment, the chimeric or humanized antibodies or fragments or V<sub>H</sub> or V<sub>L</sub> polypeptides originate or are derived from one or more rabbit antibodies, e.g., a rabbit antibody isolated from a clonal rabbit B cell population. In some embodiments, the antibody or antigen-binding fragment thereof according to the invention are humanized, such as humanized rabbit antibodies to PACAP. More particularly, anti-PACAP antibody and/or antigen-binding fragments thereof according to the invention can include human, humanized, and chimerized antibodies and fragments thereof, as well as scFvs, camelbodies, shark antibodies, nanobodies, Immunoglobulin New Antigen Receptor ("IgNAR"), fragment antigen-binding ("Fab") fragments, Fab' fragments, MetMab like antibodies, bispecific antibodies, monovalent antibody fragments, and F(ab')<sub>2</sub> fragments. 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

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another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof may be selected from the group consisting of scFvs, camelbodies, nanobodies, Immunoglobulin New Antigen Receptor ("IgNAR"), fragment antigen-binding ("Fab") fragments, Fab' fragments, MetMab  
5 like antibodies, monovalent antigen-binding fragments, and F(ab')<sub>2</sub> fragments.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof substantially or entirely lacks N-glycosylation and/or O-glycosylation. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises a human constant domain, e.g., that of IgG1, IgG2,  
10 IgG3, or IgG4 antibody or a fragment thereof. In another embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof may comprise an Fc region that has been modified to alter (enhance or impair) at least one of effector function, half-life, proteolysis, or glycosylation. For example, the Fc region may contain one or more mutations that alters or eliminates N- and/or O-glycosylation.

15 In some embodiments, the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a  $K_D$  of less than or equal to  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M, or  $10^{-13}$  M, e.g., as determined by ELISA, bio-layer interferometry ("BLI"), Kinetic Exclusion Assay (KINEXA®,  
20 Sapidyme Instruments, Boise, ID), or SPR, e.g., at 25° or 37°C. Preferably, the human, humanized, or chimerized anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a  $K_D$  of less than or equal to  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a  $K_D$  that is less than about 100 nM, less than about 40 nM, less than about 1 nM, less than about 100 pM, less than about 50 pM,  
25 or less than about 25 pM. Preferably, the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a  $K_D$  that is less than about 50 pM, less than about 40 pM, less than about 25 pM, or less than about 1 pM. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a  $K_D$  that is between about 10 pM and about 100 pM, between about 1 pM and about 100 pM, or between about 1 pM and about 10 pM. In another embodiment,  
30 the human, humanized, or chimerized anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with an off-rate ( $k_{off}$ ) of less than or equal to  $5 \times 10^{-4} \text{ s}^{-1}$ ,  $10^{-4} \text{ s}^{-1}$ ,  $5 \times 10^{-5} \text{ s}^{-1}$ , or  $10^{-5} \text{ s}^{-1}$ .

In another embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof does not substantially interact with (i.e., bind to) VIP. Preferably, the anti-PACAP antibody and/or antigen-

binding fragment thereof has stronger affinity for PACAP as compared to VIP, i.e., although there is some cross-reactivity, the antibody preferentially binds to PACAP as compared to VIP. For example, the affinity of said antibody and/or antigen-binding fragment thereof to PACAP is at least 10-fold, 30-fold, 100-fold, 300-fold, 1000-fold, 3000-fold, 10000-fold, 30000-fold, 100000-fold, 300000-fold, 1000000-fold, 3000000-fold, 10000000-fold, 30000000-fold, or stronger than the affinity of said antibody and/or antigen-binding fragments thereof to VIP (e.g., the  $K_D$  of said antibody or fragment for binding to human PACAP is 10-fold, 30-fold, 100-fold, 300-fold, 1000-fold, 3000-fold, 10000-fold, 30000-fold, 100000-fold, 300000-fold, 1000000-fold, 3000000-fold, 10000000-fold, or 30000000-fold lower than the  $K_D$  for binding to VIP).

10

In some aspects, the invention relates to an isolated antibody or antigen-binding fragment thereof that competes for binding to PACAP with an antibody or antigen-binding fragment thereof disclosed herein. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof will specifically bind to the linear or conformational epitope(s) and/or compete for binding to the same linear or conformational epitope(s) on human PACAP as an anti-PACAP antibody selected from the group consisting of Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H, Ab21.H2, Ab21.H3, Ab21.H4, Ab21, Ab22, and Ab23, preferably Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H, Ab21.H2, Ab21.H3, or Ab21.H4 (the specific amino acid sequences of the variable and constant regions of these anti-PACAP antibodies, and the nucleic acids that encode for such variable and constant regions, and the epitopes bound thereby as determined using alanine scanning methods are disclosed *infra*).

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H or Ab10.H3. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H. In a preferred embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H3.

Also, the invention encompasses an anti-PACAP antibody and/or antigen-binding fragment that may comprise at least 2; at least 3; at least 4; at least 5; or all 6 complementarity determining regions

(“CDRs”) of an anti-PACAP antibody that may comprise Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions (“CDRs”) of the anti-PACAP antibody Ab10.H or Ab10.H3. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions (“CDRs”) of the anti-PACAP antibody Ab10.H. In a preferred embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions (“CDRs”) of the anti-PACAP antibody Ab10.H3.

10

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab21.H, Ab21.H2, Ab21.H3, or Ab21.H4. Also, the invention encompasses an anti-PACAP antibody and/or antigen-binding fragment that may comprise at least 2; at least 3; at least 4; at least 5; or all 6 complementarity determining regions (“CDRs”) of an anti-PACAP antibody that may comprise Ab21.H, Ab21.H2, Ab21.H3, or Ab21.H4.

15

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab22 or Ab23. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions (“CDRs”) of an anti-PACAP antibody selected from Ab22 or Ab23.

20

In some embodiments, the present invention provides an anti-PACAP antibody and/or antigen-binding fragment thereof, which is preferably a human, humanized, or chimerized anti-PACAP antibody and/or antigen-binding fragment thereof, comprising at least 2 complementarity determining regions (“CDRs”), or at least 3 CDRs, or at least 4 CDRs, or at least 5 CDRs, or all six CDRs of an anti-PACAP antibody selected from the group consisting of Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H, Ab21.H2, Ab21.H3, Ab21.H4, Ab21, Ab22, and Ab23, preferably Ab10.H or Ab10.H3. In instances where all 6 CDRs are not present, preferably at least the  $V_H$  CDR3 and  $V_L$  CDR3 are present. In exemplary embodiments, the antibody and/or antigen-binding fragment thereof comprises the variable heavy (“ $V_H$ ”) chain and/or the variable light (“ $V_L$ ”) chain of one of Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H, Ab21.H2, Ab21.H3, Ab21.H4, Ab21, Ab22, and Ab23, preferably Ab10.H or Ab10.H3.

25

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Also, in some embodiments, the anti-PACAP antibody and/or antigen-binding fragment thereof may comprise sequence variants of any of the disclosed antibodies which are modified by mutagenesis, e.g., affinity maturation to alter one or more properties such as binding affinity or immunogenicity.

5

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 antigen-binding 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 antigen-binding 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.

10

15 In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises sequence variants having at least 90% or greater sequence homology to any of Ab10.H or Ab10.H3, such as 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 of Ab10.H or Ab10.H3. In one embodiment, the anti-PACAP antibody and/or antigen-binding  
20 fragment thereof comprises sequence variants having at least 90% or greater sequence homology to any of Ab10.H, such as 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 of Ab10.H. In one embodiment, the sequence variants differ by conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For  
25 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.

In some expression systems, the heavy chain may be cleaved in the C-terminal end, so that the C-terminal lysine (Lys, K) is cleaved off. An example of such an expression system are the widely used  
30 CHO cells. Thus, in one embodiment, the anti-PACAP antibody comprises a heavy chain or a heavy chain constant region as herein described, wherein the C-terminal lysine (Lys, K) has been cleaved off, i.e. wherein the C-terminal lysine (Lys, K) is absent.

The present invention also contemplates an anti-PACAP antibody 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 an antibody comprising the combination of any of the variable light chain and variable  
5 heavy chain sequences described herein, and further contemplates an antibody resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is attached to  
10 one or more functional moieties. The antibody and/or antigen-binding fragment 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. In one embodiment, the anti-  
15 PACAP antibody and/or antigen-binding fragment thereof is directly or indirectly attached to another moiety, such as a detectable label or therapeutic agent.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is attached to at least one effector moiety, e.g., which comprises a chemical linker. In another embodiment, the anti-  
20 PACAP antibody and/or antigen-binding fragment thereof is attached to one or more detectable moieties, e.g., which comprise a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixtures thereof.

The antibody and/or antigen-binding fragment thereof may also be chemically modified to provide  
25 additional advantages such as increased solubility, stability and circulating time (*in vivo* half-life) of the polypeptide, or decreased immunogenicity (See U.S. Patent 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 antibody and/or antigen-binding fragment thereof may be modified at random positions within  
30 the molecule, or at predetermined positions within the molecule and may include one, two, three, or more attached chemical moieties. 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

5 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.

10 Patent No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.*, 56:59-72 (1996); Vorobjev et al., *Nucleosides and 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. 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, disclosing a method of coupling PEG to G-CSF; and Malik et al., *Exp. Hematol.*, 20:1028-

15 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

20 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. 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,

25 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).

30 Alternatively, the antibody and/or antigen-binding fragment 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. Patent No. 5,876,969, EP 0 413 622, and U.S. Patent No. 5,766,883, herein incorporated by reference in their entirety)), or other circulating blood proteins such as transferrin or ferritin. In a preferred embodiment, the polypeptide and/or antibody of the present

invention (including fragments or variants thereof) is 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 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.

5

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

10

15 Methods are known in the art for conjugating an antibody or antigen-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).

20 Moreover, the present invention encompasses a composition suitable for therapeutic and/or prophylactic use comprising a therapeutically and/or prophylactically effective amount of at least one anti-PACAP antibody and/or antigen-binding fragment thereof as described herein. In particular, compositions and dosage forms containing the subject anti-PACAP antibody and/or antigen-binding fragment thereof for use in treating and/or preventing opioid-induced pain are provided herein. The composition may be suitable for subcutaneous administration, intra-muscular administration, and/or intravenous administration. The composition may be lyophilized, stabilized, and/or formulated for administration by injection. In some embodiments, the composition further comprises a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, or mixture thereof.

25

30 The present invention further contemplates an isolated nucleic acid sequence or nucleic acid sequences encoding an anti-PACAP antibody and/or antigen-binding fragment thereof described herein, as well as a vector or vectors containing these isolated nucleic acid sequence or sequences.



Additionally, the invention provides a host cell comprising these isolated nucleic acid sequence or sequences or the vector or set forth above. Said host cell may be a mammalian, bacterial, fungal, yeast, avian, amphibian, plant or insect cell, or is a CHO cell. Additionally, said CHO cell may be selected from one of the following subclones or sub-cell lines: DP12 (CHO K1 dhfr-) cell line, NS0 cells, CHO-DXB11 (CHO-DUKX), CHO-pro3, CHO-DG44, CHO 1-15, CHO DP-12, Lec2, M1WT3, Lec8, or pgsA-745. Also, said host cell may be a filamentous fungus or a yeast, e.g., selected from the following genera: *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces* preferably *Pichia* and more preferably *Pichia pastoris*, *Pichia methanolica* or *Hansenula polymorpha* (*Pichia angusta*); or said host cell may be a mammalian cell, e.g., selected from baby hamster kidney ("BHK") cells; Chinese hamster ovary ("CHO") cells; mouse Sertoli cells ("TM4" cells); African green monkey kidney cells ("VERO-76" cells); human cervical carcinoma ("HELA") cells; canine kidney cells ("MDCK"); buffalo rat liver ("BRL") cells; human lung cells; human liver ("Hep G2") cells; mouse mammary tumor ("MMT") cells; TRI cells; MRC 5 cells; and FS4 cells. In one embodiment, the host cell is an eukaryotic host cell that is mammalian, selected from the group consisting of baby hamster kidney ("BHK") cells; Chinese hamster ovary ("CHO") cells; mouse Sertoli cells ("TM4" cells); African green monkey kidney cells ("VERO-76" cells); human cervical carcinoma ("HELA") cells; canine kidney cells ("MDCK"); buffalo rat liver ("BRL") cells; human lung cells; human liver ("Hep G2") cells; mouse mammary tumor ("MMT") cells; TRI cells; MRC 5 cells; and FS4 cells. Preferably, the mammalian host cell is a CHO cell. More preferably, the mammalian host cell is a CHO K1 cell. The host cell may be a prokaryotic cell, i.e., bacterial cell, or a eukaryotic cell, including a mammalian, fungal, yeast, avian, or insect cell. In one embodiment, the host cell is a filamentous fungus or is a yeast cell. Preferably, the yeast species is of the genus *Pichia*. Most preferably, the species of *Pichia* is selected from *Pichia pastoris*, *Pichia methanolica*, and *Hansenula polymorpha* (*Pichia angusta*).

#### Exemplary Anti-PACAP Antibody Polypeptide Sequences

The present invention may be performed using any anti-PACAP Antibody. Exemplary anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, and the specific CDRs thereof are identified in this section. For convenience, each exemplified antibody or antigen-binding fragment thereof, and corresponding sequences are separately identified by a specific nomenclature, i.e., Ab10, Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6 Ab20, Ab21, Ab21.H, Ab21.H2, Ab21.H3, Ab21.H4, Ab22, and Ab23.

Exemplary anti-PACAP antibodies and/or antigen-binding fragments thereof suitable for use in this invention comprise a V<sub>H</sub> chain having an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, 99 or 100% sequence identity to a V<sub>H</sub> chain selected from SEQ ID NOs: 962, 1282, 1322, 1362, 1402, 1442, 1202, 1482, 1522, and 1562, and/or a V<sub>L</sub> chain having an amino acid sequence with at least 80,  
5 85, 90, 95, 96, 97, 98, 99, or 100% sequence identity to a V<sub>L</sub> chain selected from selected from SEQ ID NOs: 982, 1302, 1342, 1382, 1422, 1462, 1222, 1502, 1542, and 1582, and/or at least 2, 3, 4, 5, or all 6 CDRs comprised therein.

In one embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof comprises  
10 a V<sub>H</sub> chain having an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, 99 or 100% sequence identity to a V<sub>H</sub> chain selected from SEQ ID NOs: 962 or 1322, and/or a V<sub>L</sub> chain having an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, 99, or 100% sequence identity to a V<sub>L</sub> chain selected from selected from SEQ ID NOs: 982 or 1342, and/or at least 2, 3, 4, 5, or all 6 CDRs comprised therein.  
In one embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof comprises  
15 a V<sub>H</sub> chain having an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, 99 or 100% sequence identity to a V<sub>H</sub> chain selected from SEQ ID NOs: 962, and/or a V<sub>L</sub> chain having an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, 99, or 100% sequence identity to a V<sub>L</sub> chain selected from selected from SEQ ID NOs: 982, and/or at least 2, 3, 4, 5, or all 6 CDRs comprised therein. In one  
embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof comprises a V<sub>H</sub>  
20 chain having an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, 99 or 100% sequence identity to a V<sub>H</sub> chain selected from SEQ ID NOs: 1322, and/or a V<sub>L</sub> chain having an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, 99, or 100% sequence identity to a V<sub>L</sub> chain selected from selected from SEQ ID NOs: 1342, and/or at least 2, 3, 4, 5, or all 6 CDRs comprised therein.

25 In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises 2, 3, 4, 5 or all 6 complementarity determining regions ("CDRs") of Ab21.H, Ab21.H2, Ab21.H3, Ab21.H4, Ab22, or Ab23 or all 6 complementarity determining regions of Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6. In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof is humanized and comprises all 6 CDRs of an anti-PACAP antibody selected from Ab10.H,  
30 Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21.H, Ab21.H2, Ab21.H3, Ab21.H4, Ab22, or Ab23.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues wherein said epitope may be selected from the group consisting of:

- i. at least one of residues 22, 23, 27, 28, and 31 of a human PACAP;
- ii. at least one of residues 12, 20, 23, 24, 26, 27, and 28 of a human PACAP;
- iii. at least one of residues 19, 22, 23, and 27 of a human PACAP;
- iv. at least two of the residues of (i), (ii), or (iii);
- 5 v. at least three of the residues of (i), (ii), or (iii);
- vi. at least four of the residues of (i), (ii), or (iii);
- vii. at least five of the residues of (i) or (ii);
- viii. at least six of the residues of (ii);
- ix. at least seven of the residues of (ii); and
- 10 x. at least the residues 23, 27, and 28, of a human PACAP, and optionally, between one to six of the additional residues of (i) and/or (ii).

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues that is present in human wild-type PACAP38) but not human wild-type human PACAP27. Also, in one embodiment the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues, wherein said epitope consists of the residues of any one of (i), (ii), or (iii). Also, in one embodiment the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues) that is present in human wild-type PACAP38 and in human wild-type human PACAP27. Said epitope may be identified by e.g. alanine scanning, or by another art recognized method.

#### 25 **Antibody Ab10.H**

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 961 which consists of the heavy chain variable region of SEQ ID NO: 962 linked to the heavy chain constant region of SEQ ID NO: 970.

30

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSYYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDNK  
NTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLVTVSS (SEQ ID NO: 962).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
5 having binding specificity to PACAP that bind the same epitope as Ab10.H, and that contain a constant  
heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising  
the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT  
QTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE  
10 VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF  
SCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO: 970).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
15 having binding specificity to PACAP that contain a light chain sequence comprising the sequence of  
SEQ ID NO: 981 which consists of the light chain variable region of SEQ ID NO: 982 linked to the light  
chain constant region of SEQ ID NO: 990.

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
20 having binding specificity to PACAP that contain a variable light chain sequence comprising the  
sequence set forth below:

DAQLTQSPSTLSASVIGDRVITCQSSSEVYGNLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISL  
QPDDFATYYCAGGDISEGVAFGGGTKVEIKR (SEQ ID NO: 982).

25 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
having binding specificity to PACAP, that bind the same epitope as Ab10.H, and that contain a constant  
light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPRKAVQWVKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKAD  
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 990).

30

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of  
SEQ ID NO: 964; SEQ ID NO: 966; and SEQ ID NO: 968, which correspond to the CDRs (hypervariable  
regions) of the heavy chain sequence of SEQ ID NO: 961, or which contain the variable heavy chain

sequence of SEQ ID NO: 962, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 984; SEQ ID NO: 986; and SEQ ID NO: 988, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 981, or which contain the variable light chain sequence of SEQ ID NO: 982, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto.

In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 963; SEQ ID NO: 965; SEQ ID NO: 967; and SEQ ID NO: 969, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 961, or the variable heavy chain sequence of SEQ ID NO: 962, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 983; SEQ ID NO: 985; SEQ ID NO: 987; and SEQ ID NO: 989, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 981, or the variable light chain sequence of SEQ ID NO: 982, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 961, or SEQ ID NO: 962, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 981, or SEQ ID NO: 982, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 964; SEQ ID NO: 966; and SEQ ID NO: 968, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 961, or the variable heavy chain sequence of SEQ ID NO: 962, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 984; SEQ ID NO: 986; and SEQ ID NO: 988, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 981, or the variable light chain sequence of SEQ ID NO: 982, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 963; SEQ ID NO: 965; SEQ ID NO: 967; and SEQ ID NO: 969, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 961, or the variable heavy chain sequence of SEQ ID NO: 962, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 983; SEQ ID NO: 985; SEQ ID NO: 987; and SEQ ID NO: 989, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 981, or the variable light chain sequence of SEQ ID NO: 982, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 962; the variable light chain region of SEQ ID NO: 982; the complementarity determining regions (SEQ ID NO: 964; SEQ ID NO: 966; and SEQ ID NO: 968) of the variable heavy chain region of SEQ ID NO: 962; and the complementarity determining regions (SEQ

ID NO: 984; SEQ ID NO: 986; and SEQ ID NO: 988) of the variable light chain region of SEQ ID NO: 982, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain  
5 region of SEQ ID NO: 962; the variable light chain region of SEQ ID NO: 982; the framework regions (SEQ ID NO: 963; SEQ ID NO: 965; SEQ ID NO: 967; and SEQ ID NO: 969) of the variable heavy chain region of SEQ ID NO: 962; and the framework regions (SEQ ID NO: 983; SEQ ID NO: 985; SEQ ID NO: 987; and SEQ ID NO: 989) of the variable light chain region of SEQ ID NO: 982, or sequences that are at least 90% or 95% identical thereto.

10

In another embodiment of the invention, the anti-PACAP antibody is Ab10.H, comprising, or alternatively consisting of, SEQ ID NO: 961 and SEQ ID NO: 981, or SEQ ID NO: 962 and SEQ ID NO: 982, or an antibody or antigen-binding fragment comprising the CDRs of Ab10.H and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with  
15 Ab10.H in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab10.H, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab10.H.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively  
20 consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 962 and the variable light chain sequence of SEQ ID NO: 982, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 962 and/or SEQ ID NO: 982 that retain the binding  
25 specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H. In another embodiment of the invention, anti-PACAP antibodies such as Ab10.H and Fab fragments may be produced via expression in mammalian cells, such as CHO, NSO, or HEK 293 cells, fungal, insect,  
30 or microbial systems, such as yeast cells (for example haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab10.H, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth  
5 above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies and/or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1  
10 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain comprising an amino acid sequence with  
15 at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 962, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 982. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 982. More  
20 specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 981.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof  
25 according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 962 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (b) a variable light chain comprising  
30 an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 982 and comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and/or (b) a variable light chain having the amino acid



sequence of SEQ ID NO: 982. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 982. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a)

5 a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 961 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 981 and comprising a CDR1 sequence consisting of SEQ ID NO:

10 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 981. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID

15 NO: 961, and (b) a light chain having the amino acid sequence of SEQ ID NO: 981.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 962 and comprising a CDR1 sequence consisting

20 of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 982 and comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;

25 b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 982;

c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 982;

d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97,

30 98, or 99% sequence identity to SEQ ID NO: 961 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 981 and comprising a CDR1 sequence consisting of

SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;

- e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 981; and/or
- 5 f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 981.

#### **Antibody Ab21**

- 10 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 841 which consists of the heavy chain variable region of SEQ ID NO: 842 linked to the heavy chain constant region of SEQ ID NO: 850.

- 15 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLCTVSGIDLSSYYMTWVRQAPGKGLEWVGFDAGGSAYYATWAKGRFTISKASTTVD  
LKITSPTTEDTATYFCARDLDLWGPGLTVTVSS (SEQ ID NO: 842).

- 20 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab21, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

- ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- 25 QTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE
- VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
- VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
- SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 850).

- 30 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 861 which consists of the light chain variable region of SEQ ID NO: 862 linked to the light chain constant region of SEQ ID NO: 870.

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

AAVLTQTPSPVSAAVGGTVSISCKSSESVYGDYLAWFQQKPGQPPKQLIYDASTLASGVPSRFKSGSGTQFTLTIS  
5 GVQCDDAATYYCAGGYVSAGVAFGGGTEVVVKR (SEQ ID NO: 862).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab21, and that contain a constant light chain sequence comprising the sequence set forth below:

10 TVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKAD  
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 870).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of  
15 SEQ ID NO: 844; SEQ ID NO: 846; and SEQ ID NO: 848, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 841, or which contain the variable heavy chain sequence of SEQ ID NO: 842, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 864; SEQ ID NO: 866; and SEQ ID NO: 868, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 861, or which contain the variable  
20 light chain sequence of SEQ ID NO: 862, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences  
25 set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 843; SEQ ID NO: 845; SEQ ID NO: 847; and SEQ ID NO: 849, which correspond to the FRs (constant regions) of the heavy  
30 chain sequence of SEQ ID NO: 841, or the variable heavy chain sequence of SEQ ID NO: 842, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 863; SEQ ID NO: 865; SEQ ID NO: 867; and SEQ ID NO: 869, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 861, or the variable light chain sequence of SEQ ID NO: 862, or combinations of these

polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

5 In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

10 In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 841, or SEQ ID NO: 842, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 861, or SEQ  
15 ID NO: 862, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 844; SEQ ID NO: 846; and SEQ ID NO: 848, which correspond to  
20 the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 841, or the variable heavy chain sequence of SEQ ID NO: 842, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the  
25 polypeptide sequences of SEQ ID NO: 864; SEQ ID NO: 866; and SEQ ID NO: 868, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 861, or the variable light chain sequence of SEQ ID NO: 862, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof  
30 having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 843; SEQ ID NO: 845; SEQ ID NO: 847; and SEQ ID NO: 849, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 841, or the variable heavy chain sequence of SEQ ID NO: 842, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 863; SEQ ID NO: 865; SEQ ID NO: 867; and SEQ ID NO: 869, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 861, or the variable light chain sequence of SEQ ID NO: 862, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 842; the variable light chain region of SEQ ID NO: 862; the complementarity determining regions (SEQ ID NO: 844; SEQ ID NO: 846; and SEQ ID NO: 848) of the variable heavy chain region of SEQ ID NO: 842; and the complementarity determining regions (SEQ ID NO: 864; SEQ ID NO: 866; and SEQ ID NO: 868) of the variable light chain region of SEQ ID NO: 862, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 842; the variable light chain region of SEQ ID NO: 862; the framework regions (SEQ ID NO: 843; SEQ ID NO: 845; SEQ ID NO: 847; and SEQ ID NO: 849) of the variable heavy chain region of SEQ ID NO: 842; and the framework regions (SEQ ID NO: 863; SEQ ID NO: 865; SEQ ID NO: 867; and SEQ ID NO: 869) of the variable light chain region of SEQ ID NO: 862, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab21, comprising, or alternatively consisting of, SEQ ID NO: 841 and SEQ ID NO: 861, or SEQ ID NO: 842 and SEQ ID NO: 862, or an antibody or antigen-binding fragment comprising the CDRs of Ab21 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab21 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab21, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab21.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab21, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 842 and the variable light chain sequence of SEQ ID NO: 862, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 842 and/or SEQ ID NO: 862 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab21. In another embodiment of the invention, anti-PACAP antibodies such as Ab21 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab21, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In one embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 844; a CDR2 sequence consisting of SEQ ID NO: 846; and a CDR3 sequence consisting of SEQ ID NO: 848; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 864; a CDR2 sequence consisting of SEQ ID NO: 866; and a CDR3 sequence consisting of SEQ ID NO: 868. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 842, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 862. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 842, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 862. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain

having the amino acid sequence of SEQ ID NO: 841, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 861.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

- 5 a. a variable heavy chain comprising the CDR1 sequence consisting of SEQ ID NO: 844; a CDR2 sequence consisting of SEQ ID NO: 846; and a CDR3 sequence consisting of SEQ ID NO: 848; and/or
- b. a variable light chain comprising the CDR1 sequence consisting of SEQ ID NO: 864; a CDR2 sequence consisting of SEQ ID NO: 866; and a CDR3 sequence consisting of SEQ ID NO: 868,
- 10 wherein optionally said antibody comprises:
  - (a) (i) the variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 842, and/or (ii) the variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 862;
  - 15 (b) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 842, or (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 862;
  - (c) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 842, and (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 862;
  - (d) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 841, and/or (ii) the
  - 20 light chain having the amino acid sequence of SEQ ID NO: 861; or
  - (e) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 841, and (ii) the light chain having the amino acid sequence of SEQ ID NO: 861.

#### **Antibody Ab21.H**

- 25 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 1201 which consists of the heavy chain variable region of SEQ ID NO: 1202 linked to the heavy chain constant region of SEQ ID NO: 1210.
- 30 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:  
 EVQLVESGGGLVQPGGSLRLSCAASGIDLSSYYMTWVRQAPGKGLEWIGFIDAGGSAYYATWAKGRFTISRDNSK  
 NTVYLQMNSLR AEDTAVYFCARDLDLWGQGTLVTVSS (SEQ ID NO: 1202).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab21.H, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

5     ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVVPSSSLGT  
       QTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE  
       VKFNWYVDGVEVHNAKTKPREEQYASTYRVSVLTVHLQDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
       VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSLKLTVDKSRWQQGNV  
 10     SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1210).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1221 which consists of the light chain variable region of SEQ ID NO: 1222 linked to the light chain constant region of SEQ ID NO: 1230.

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In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

20     DAQLTQSPSTLSASVGDRTITCKSSSESVYGDYLAWFQQKPGKAPKQLIYDASTLASGVPSRFSGSGSGTEFTLTISL  
       QPDDFATYYCAGGYVSAGVAFGGGTKVEIKR (SEQ ID NO: 1222).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab21.H, and that contain a constant light chain sequence comprising the sequence set forth below:

25     TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKAD  
       YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1230).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1204; SEQ ID NO: 1206; and SEQ ID NO: 1208, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1201, or which contain the variable heavy chain sequence of SEQ ID NO: 1202, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1224; SEQ ID NO: 1226; and SEQ ID NO: 1228, which correspond to the CDRs

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(hypervariable regions) of the light chain sequence of SEQ ID NO: 1221, or which contain the variable light chain sequence of SEQ ID NO: 1222, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding  
5 fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof  
10 comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1203; SEQ ID NO: 1205; SEQ ID NO: 1207; and SEQ ID NO: 1209, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1201, or the variable heavy chain sequence of SEQ ID NO: 1202, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1223; SEQ ID NO: 1225; SEQ ID NO: 1227; and SEQ ID NO: 1229, which correspond to the FRs (constant regions) of the light  
15 chain sequence of SEQ ID NO: 1221, or the variable light chain sequence of SEQ ID NO: 1222, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments  
20 thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments  
25 thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1201, or SEQ ID NO: 1202, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1221, or SEQ  
30 ID NO: 1222, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1204; SEQ ID NO: 1206; and SEQ ID NO: 1208, which correspond

to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1201, or the variable heavy chain sequence of SEQ ID NO: 1202, or sequences that are at least 90% or 95% identical thereto.

5 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1224; SEQ ID NO: 1226; and SEQ ID NO: 1228, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1221, or the variable light chain sequence of SEQ ID NO: 1222, or sequences that are at least 90% or 95% identical thereto.

10 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1203; SEQ ID NO: 1205; SEQ ID NO: 1207; and SEQ ID NO: 1209, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1201, or the variable heavy chain sequence of SEQ ID NO: 1202, or sequences that are at least 90% or 95% identical thereto.

15 In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1223; SEQ ID NO: 1225; SEQ ID NO: 1227; and SEQ ID NO: 1229, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1221, or the variable light chain sequence of SEQ ID NO: 1222, or sequences that are at least 90% or 95% identical thereto.

25 The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1202; the variable light chain region of SEQ ID NO: 1222; the complementarity determining regions (SEQ ID NO: 1204; SEQ ID NO: 1206; and SEQ ID NO: 1208) of the variable heavy chain region of SEQ ID NO: 1202; and the complementarity determining regions (SEQ ID NO: 1224; SEQ ID NO: 1226; and SEQ ID NO: 1228) of the variable light chain region of SEQ ID NO: 1222, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable

heavy chain region of SEQ ID NO: 1202; the variable light chain region of SEQ ID NO: 1222; the framework regions (SEQ ID NO: 1203; SEQ ID NO: 1205; SEQ ID NO: 1207; and SEQ ID NO: 1209) of the variable heavy chain region of SEQ ID NO: 1202; and the framework regions (SEQ ID NO: 1223; SEQ ID NO: 1225; SEQ ID NO: 1227; and SEQ ID NO: 1229) of the variable light chain region of SEQ ID NO: 1222, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab21.H, comprising, or alternatively consisting of, SEQ ID NO: 1201 and SEQ ID NO: 1221, or SEQ ID NO: 1202 and SEQ ID NO: 1222, or an antibody or antigen-binding fragment comprising the CDRs of Ab21.H and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab21.H in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab21.H, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab21.H.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1202 and the variable light chain sequence of SEQ ID NO: 1222, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1202 and/or SEQ ID NO: 1222 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab21.H. In another embodiment of the invention, anti-PACAP antibodies such as Ab21.H and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab21.H, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 1204; a CDR2 sequence consisting of SEQ ID NO: 1206; and a CDR3 sequence consisting of SEQ ID NO: 1208; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1224; a CDR2 sequence consisting of SEQ ID NO: 1226; and a CDR3 sequence consisting of SEQ ID NO: 1228. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1202, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1222. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1202, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1222. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1201, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1221.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1202 and comprising a CDR1 sequence consisting of SEQ ID NO: 1204; a CDR2 sequence consisting of SEQ ID NO: 1206; and a CDR3 sequence consisting of SEQ ID NO: 1208; and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1222 and comprising a CDR1 sequence consisting of SEQ ID NO: 1224; a CDR2 sequence consisting of SEQ ID NO: 1226; and a CDR3 sequence consisting of SEQ ID NO: 1228. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1202, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1222. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1202, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1222. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98,

or 99% sequence identity to SEQ ID NO: 1201 and comprising a CDR1 sequence consisting of SEQ ID NO: 1204; a CDR2 sequence consisting of SEQ ID NO: 1206; and a CDR3 sequence consisting of SEQ ID NO: 1208; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1221 and comprising a CDR1 sequence consisting of

5 SEQ ID NO: 1224; a CDR2 sequence consisting of SEQ ID NO: 1226; and a CDR3 sequence consisting of SEQ ID NO: 1228. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1201, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1221. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid

10 sequence of SEQ ID NO: 1201, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1221.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

a. a variable heavy chain comprising the CDR1 sequence consisting of SEQ ID NO: 1204; a

15 CDR2 sequence consisting of SEQ ID NO: 1206; and a CDR3 sequence consisting of SEQ ID NO: 1208; and/or

b. a variable light chain comprising the CDR1 sequence consisting of SEQ ID NO: 1224; a CDR2 sequence consisting of SEQ ID NO: 1226; and a CDR3 sequence consisting of SEQ ID NO: 1228, wherein optionally said antibody comprises:

20 (a) (i) the variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1202, and/or (ii) the variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1222;

(b) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1202, or (ii)

25 the variable light chain having the amino acid sequence of SEQ ID NO: 1222;

(c) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1202, and (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 1222;

(d) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1201, and/or (ii) the light chain having the amino acid sequence of SEQ ID NO: 1221; or

30 (e) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1201, and (ii) the light chain having the amino acid sequence of SEQ ID NO: 1221.

#### Antibody Ab22

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 881 which consists of the heavy chain variable region of SEQ ID NO: 882 linked to the heavy chain constant region of SEQ ID NO: 890.

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In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

QEQLVESGGGLVQPEGSLTCTASGDFSSNAMCWVRQAPGKGLEWIGSIYNADGKNYYAIWAKGRFTISRSS

10 TTVTLQMTSLTAADTATYFCARDFDLWGQGLTVTVSS (SEQ ID NO: 882).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab22, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising

15 the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT  
QTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE  
VKFNWYVDGVEVHNAKTKPREEQYASTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF

20 SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 890).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 901 which consists of the light chain variable region of SEQ ID NO: 902 linked to the light

25 chain constant region of SEQ ID NO: 910.

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

AAVLTQTPSPVSAAVGGTVTINCQSSQSVYDNDWLAWFQKPGQPPKLLIYLTSTLASGVPSRFSGSGSGTQFTLTI  
SGVQCDDAATYYCLGGYDEGDTHVFGGGTEVVVKR (SEQ ID NO: 902).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab22, and that contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKAD

5 YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 910).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 884; SEQ ID NO: 886; and SEQ ID NO: 888, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 881, or which contain the variable heavy chain sequence of SEQ ID NO: 882, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 904; SEQ ID NO: 906; and SEQ ID NO: 908, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 901, or which contain the variable light chain sequence of SEQ ID NO: 902, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

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The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 883; SEQ ID NO: 885; SEQ ID NO: 887; and SEQ ID NO: 889, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 881, or the variable heavy chain sequence of SEQ ID NO: 882, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 903; SEQ ID NO: 905; SEQ ID NO: 907; and SEQ ID NO: 909, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 901, or the variable light chain sequence of SEQ ID NO: 902, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

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In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy

chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

5 In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 881, or SEQ ID NO: 882, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 901, or SEQ ID NO: 902, or polypeptides that are at least 90% or 95% identical thereto.

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In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 884; SEQ ID NO: 886; and SEQ ID NO: 888, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 881, or the variable heavy chain sequence of SEQ ID NO: 882, or sequences that are at least 90% or 95% identical thereto.

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In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 904; SEQ ID NO: 906; and SEQ ID NO: 908, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 901, or the variable light chain sequence of SEQ ID NO: 902, or sequences that are at least 90% or 95% identical thereto.

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In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 883; SEQ ID NO: 885; SEQ ID NO: 887; and SEQ ID NO: 889, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 881, or the variable heavy chain sequence of SEQ ID NO: 882, or sequences that are at least 90% or 95% identical thereto.

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30 In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 903; SEQ ID NO: 905; SEQ ID NO: 907; and SEQ ID NO: 909, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO:



901, or the variable light chain sequence of SEQ ID NO: 902, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 882; the variable light chain region of SEQ ID NO: 902; the complementarity determining regions (SEQ ID NO: 884; SEQ ID NO: 886; and SEQ ID NO: 888) of the variable heavy chain region of SEQ ID NO: 882; and the complementarity determining regions (SEQ ID NO: 904; SEQ ID NO: 906; and SEQ ID NO: 908) of the variable light chain region of SEQ ID NO: 902, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 882; the variable light chain region of SEQ ID NO: 902; the framework regions (SEQ ID NO: 883; SEQ ID NO: 885; SEQ ID NO: 887; and SEQ ID NO: 889) of the variable heavy chain region of SEQ ID NO: 882; and the framework regions (SEQ ID NO: 903; SEQ ID NO: 905; SEQ ID NO: 907; and SEQ ID NO: 909) of the variable light chain region of SEQ ID NO: 902, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab22, comprising, or alternatively consisting of, SEQ ID NO: 881 and SEQ ID NO: 901, or SEQ ID NO: 882 and SEQ ID NO: 902, or an antibody or antigen-binding fragment comprising the CDRs of Ab22 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab22 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab22, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab22.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab22, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 882 and the variable light chain sequence of SEQ ID NO: 902, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions,

deletions, and variants of SEQ ID NO: 882 and/or SEQ ID NO: 902 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab22.

5 In another embodiment of the invention, anti-PACAP antibodies such as Ab22 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

10 In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab22, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

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In one embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 884; a CDR2 sequence consisting of SEQ ID NO: 886; and a CDR3 sequence

20 consisting of SEQ ID NO: 888; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 904; a CDR2 sequence consisting of SEQ ID NO: 906; and a CDR3 sequence consisting of SEQ ID NO: 908. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 882, and/or (b) a variable light chain comprising  
25 an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 902. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 882, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 902. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain  
30 having the amino acid sequence of SEQ ID NO: 881, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 901.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

- a. a variable heavy chain comprising the CDR1 sequence consisting of SEQ ID NO: 884; a CDR2 sequence consisting of SEQ ID NO: 886; and a CDR3 sequence consisting of SEQ ID NO: 888; and/or
- b. a variable light chain comprising the CDR1 sequence consisting of SEQ ID NO: 904; a CDR2 sequence consisting of SEQ ID NO: 906; and a CDR3 sequence consisting of SEQ ID NO: 908, wherein optionally said antibody comprises:
- (a) (i) the variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 882, and/or (ii) the variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 902;
- (b) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 882, or (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 902;
- (c) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 882, and (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 902;
- (d) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 881, and/or (ii) the light chain having the amino acid sequence of SEQ ID NO: 901; or
- (e) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 881, and (ii) the light chain having the amino acid sequence of SEQ ID NO: 901.

#### 20 **Antibody Ab23**

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 921 which consists of the heavy chain variable region of SEQ ID NO: 922 linked to the heavy chain constant region of SEQ ID NO: 930.

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In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLCTVSGFSLNNYAMSWVRQAPGKGLEWIGIMGVNDITYYASWAKGRFTISKSTTV

30

DLKMTSLTTEDTATYFCTREIRDDGDSSDKLWGPGLTVTVSS (SEQ ID NO: 922).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab23, and that contain a constant

heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT  
QTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE  
5 VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFLLYSKLTVDKSRWQQGNVF  
SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 930).

10 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 941 which consists of the light chain variable region of SEQ ID NO: 942 linked to the light chain constant region of SEQ ID NO: 950.

15 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

AIKMTQTPSSVSAAVGGTVTINCQASEDIYTNLAWYQQKPGQPPNLLIYDASDLASGVPSRFSGSGDGTQFTLTISA  
VQCEDAATYYCQGVAWSSNTGYGSAFGGGTEVVVKR (SEQ ID NO: 942).

20 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab23, and that contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLTLSKAD  
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 950).

25

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 924; SEQ ID NO: 926; and SEQ ID NO: 928, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 921, or which contain the variable heavy chain sequence of SEQ ID NO: 922, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 944; SEQ ID NO: 946; and SEQ ID NO: 948, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 941, or which contain the variable light chain sequence of SEQ ID NO: 942, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical

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thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

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The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 923; SEQ ID NO: 925; SEQ ID NO: 927; and SEQ ID NO: 929, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 921, or the variable heavy chain sequence of SEQ ID NO: 922, and/or

10 one, two, three, or four of the polypeptide sequences of SEQ ID NO: 943; SEQ ID NO: 945; SEQ ID NO: 947; and SEQ ID NO: 949, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 941, or the variable light chain sequence of SEQ ID NO: 942, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

15

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least

20 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 921, or SEQ ID NO: 922, or polypeptides that are at least 90% or 95% identical thereto. In another

25 embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 941, or SEQ ID NO: 942, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof

30 having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 924; SEQ ID NO: 926; and SEQ ID NO: 928, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 921, or the variable heavy chain sequence of SEQ ID NO: 922, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 944; SEQ ID NO: 946; and SEQ ID NO: 948, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 941, or the variable light  
5 chain sequence of SEQ ID NO: 942, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 923; SEQ ID NO: 925; SEQ ID NO: 927; and SEQ ID NO: 929,  
10 which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 921, or the variable heavy chain sequence of SEQ ID NO: 922, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments  
15 thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 943; SEQ ID NO: 945; SEQ ID NO: 947; and SEQ ID NO: 949, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 941, or the variable light chain sequence of SEQ ID NO: 942, or sequences that are at least 90% or 95% identical thereto.

20

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments:  
25 the variable heavy chain region of SEQ ID NO: 922; the variable light chain region of SEQ ID NO: 942; the complementarity determining regions (SEQ ID NO: 924; SEQ ID NO: 926; and SEQ ID NO: 928) of the variable heavy chain region of SEQ ID NO: 922; and the complementarity determining regions (SEQ ID NO: 944; SEQ ID NO: 946; and SEQ ID NO: 948) of the variable light chain region of SEQ ID NO: 942, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention,  
30 fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 922; the variable light chain region of SEQ ID NO: 942; the framework regions (SEQ ID NO: 923; SEQ ID NO: 925; SEQ ID NO: 927; and SEQ ID NO: 929) of the variable heavy chain region of SEQ ID NO: 922; and the framework regions (SEQ ID NO: 943; SEQ ID NO: 945; SEQ ID NO:

947; and SEQ ID NO: 949) of the variable light chain region of SEQ ID NO: 942, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab23, comprising, or alternatively  
5 consisting of, SEQ ID NO: 921 and SEQ ID NO: 941, or SEQ ID NO: 922 and SEQ ID NO: 942, or an antibody or antigen-binding fragment comprising the CDRs of Ab23 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab23 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab23, or an antibody that binds to the same or overlapping epitope(s) on PACAP  
10 as Ab23.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab23, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 922 and the variable  
15 light chain sequence of SEQ ID NO: 942, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 922 and/or SEQ ID NO: 942 that retain the binding specificity for PACAP.

20 In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab23. In another embodiment of the invention, anti-PACAP antibodies such as Ab23 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

25 In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab23, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth  
30 above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In one embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence

- consisting of SEQ ID NO: 924; a CDR2 sequence consisting of SEQ ID NO: 926; and a CDR3 sequence consisting of SEQ ID NO: 928; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 944; a CDR2 sequence consisting of SEQ ID NO: 946; and a CDR3 sequence consisting of SEQ ID NO: 948. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof
- 5 may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 922, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 942. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 922,
- 10 and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 942. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 921, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 941.
- 15 In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises
- a. a variable heavy chain comprising the CDR1 sequence consisting of SEQ ID NO: 924; a CDR2 sequence consisting of SEQ ID NO: 926; and a CDR3 sequence consisting of SEQ ID NO: 928; and/or
  - b. a variable light chain comprising the CDR1 sequence consisting of SEQ ID NO: 944; a
- 20 CDR2 sequence consisting of SEQ ID NO: 946; and a CDR3 sequence consisting of SEQ ID NO: 948, wherein optionally said antibody comprises:
- (a) (i) the variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 922, and/or (ii) the variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity
- 25 to SEQ ID NO: 942;
- (b) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 922, or (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 942;
  - (c) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 922, and (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 942;
- 30 (d) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 921, and/or (ii) the light chain having the amino acid sequence of SEQ ID NO: 941; or
- (e) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 921, and (ii) the light chain having the amino acid sequence of SEQ ID NO: 941.



**Antibody Ab10.H2**

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 1281 which consists of the heavy chain variable region of SEQ ID NO: 1282 linked to the heavy chain constant region of SEQ ID NO: 1290.

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLNSYYMTWVRQAPGKLEWIGFIDAGGDAYYASWAKGRFTISRDNK  
NTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLLTVSS (SEQ ID NO: 1282).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab10.H2, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT  
QTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE  
VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV  
SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1290).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1301 which consists of the light chain variable region of SEQ ID NO: 1302 linked to the light chain constant region of SEQ ID NO: 1310.

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

AVLTQSPSTLSASVGDRTITCQSSSESVYGNLAWFQQKPKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISLQ  
PDDFATYYCAGGDISEGVAFGGGTKEIKR (SEQ ID NO: 1302).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab10.H2, and that contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPRQAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD

5 YEKHKVVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1310).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1284; SEQ ID NO: 1286; and SEQ ID NO: 1288, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1281, or which contain the variable heavy chain sequence of SEQ ID NO: 1282, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1304; SEQ ID NO: 1306; and SEQ ID NO: 1308, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1301, or which contain the variable light chain sequence of SEQ ID NO: 1302, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

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The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1283; SEQ ID NO: 1285; SEQ ID NO: 1287; and SEQ ID NO: 1289, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1281, or the variable heavy chain sequence of SEQ ID NO: 1282, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1303; SEQ ID NO: 1305; SEQ ID NO: 1307; and SEQ ID NO: 1309, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1301, or the variable light chain sequence of SEQ ID NO: 1302, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

30

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy

chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

5 In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1281, or SEQ ID NO: 1282, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1301, or SEQ ID NO: 1302, or polypeptides that are at least 90% or 95% identical thereto.

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In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1284; SEQ ID NO: 1286; and SEQ ID NO: 1288, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1281, or the variable heavy chain sequence of SEQ ID NO: 1282, or sequences that are at least 90% or 95% identical thereto.

15

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1304; SEQ ID NO: 1306; and SEQ ID NO: 1308, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1301, or the variable light chain sequence of SEQ ID NO: 1302, or sequences that are at least 90% or 95% identical thereto.

20

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1283; SEQ ID NO: 1285; SEQ ID NO: 1287; and SEQ ID NO: 1289, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1281, or the variable heavy chain sequence of SEQ ID NO: 1282, or sequences that are at least 90% or 95% identical thereto.

25

30 In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1303; SEQ ID NO: 1305; SEQ ID NO: 1307; and SEQ ID NO: 1309, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO:

1301, or the variable light chain sequence of SEQ ID NO: 1302, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1282; the variable light chain region of SEQ ID NO: 1302; the complementarity determining regions (SEQ ID NO: 1284; SEQ ID NO: 1286; and SEQ ID NO: 1288) of the variable heavy chain region of SEQ ID NO: 1282; and the complementarity determining regions (SEQ ID NO: 1304; SEQ ID NO: 1306; and SEQ ID NO: 1308) of the variable light chain region of SEQ ID NO: 1302, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1282; the variable light chain region of SEQ ID NO: 1302; the framework regions (SEQ ID NO: 1283; SEQ ID NO: 1285; SEQ ID NO: 1287; and SEQ ID NO: 1289) of the variable heavy chain region of SEQ ID NO: 1282; and the framework regions (SEQ ID NO: 1303; SEQ ID NO: 1305; SEQ ID NO: 1307; and SEQ ID NO: 1309) of the variable light chain region of SEQ ID NO: 1302, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab10.H2, comprising, or alternatively consisting of, SEQ ID NO: 1281 and SEQ ID NO: 1301, or SEQ ID NO: 1282 and SEQ ID NO: 1302, or an antibody or antigen-binding fragment comprising the CDRs of Ab10.H2 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab10.H2 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab10.H2, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab10.H2.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H2, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1282 and the variable light chain sequence of SEQ ID NO: 1302, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing

additions, deletions, and variants of SEQ ID NO: 1282 and/or SEQ ID NO: 1302 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H2.

5 In another embodiment of the invention, anti-PACAP antibodies such as Ab10.H2 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

10

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab10.H2, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth  
15 above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1  
20 sequence consisting of SEQ ID NO: 1284; a CDR2 sequence consisting of SEQ ID NO: 1286; and a CDR3 sequence consisting of SEQ ID NO: 1288; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1304; a CDR2 sequence consisting of SEQ ID NO: 1306; and a CDR3 sequence consisting of SEQ ID NO: 1308. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at  
25 least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1282, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1302. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1282, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:  
30 1302. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1281, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1301.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1282 and comprising a CDR1 sequence consisting of SEQ ID NO: 1284; a CDR2 sequence consisting of SEQ ID NO: 1286; and a CDR3 sequence consisting of SEQ ID NO: 1288; and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1302 and comprising a CDR1 sequence consisting of SEQ ID NO: 1304; a CDR2 sequence consisting of SEQ ID NO: 1306; and a CDR3 sequence consisting of SEQ ID NO: 1308. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1282, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1302. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1282, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1302. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1281 and comprising a CDR1 sequence consisting of SEQ ID NO: 1284; a CDR2 sequence consisting of SEQ ID NO: 1286; and a CDR3 sequence consisting of SEQ ID NO: 1288; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1301 and comprising a CDR1 sequence consisting of SEQ ID NO: 1304; a CDR2 sequence consisting of SEQ ID NO: 1306; and a CDR3 sequence consisting of SEQ ID NO: 1308. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1281, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1301. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1281, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1301.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1282 and comprising a CDR1 sequence consisting of SEQ ID NO: 1284; a CDR2 sequence consisting of SEQ ID NO: 1286; and a CDR3 sequence consisting of SEQ ID NO: 1288; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1302 and comprising a

CDR1 sequence consisting of SEQ ID NO: 1304; a CDR2 sequence consisting of SEQ ID NO: 1306; and a CDR3 sequence consisting of SEQ ID NO: 1308;

- b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1282, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1302;
- 5 c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1282, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1302;
- d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1281 and comprising a CDR1 sequence consisting of SEQ ID NO: 1284; a CDR2 sequence consisting of SEQ ID NO: 1286; and a CDR3 sequence consisting of SEQ ID NO: 1288; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1301 and comprising a CDR1 sequence consisting of SEQ ID NO: 1304; a CDR2 sequence consisting of SEQ ID NO: 1306; and a CDR3 sequence consisting of SEQ ID NO: 1308;
- 10 e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1281, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1301; and/or
- 15 f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1281, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 1301.

#### **Antibody Ab10.H3**

- 20 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 1321 which consists of the heavy chain variable region of SEQ ID NO: 1322 linked to the heavy chain constant region of SEQ ID NO: 1330.

- 25 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSYYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDN SK  
NTVYLQMNSLRAEDTAVYFCARDLDLWGQGT LVT VSS (SEQ ID NO: 1322).

30

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab10.H3, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVPSSSLGT  
 QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE  
 VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
 VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF  
 5 SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1330).

In some expression systems, the heavy chain may be cleaved in the C-terminal end, so that the C-terminal lysine (Lys, K) is cleaved off. An example of such an expression system is the widely used CHO cells. In such system the resulting heavy chain constant region sequence will comprise the following  
 10 sequence:  
 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVPSSSLGT  
 QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE  
 VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
 VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF  
 15 SCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO.: 1603).

Thus, in one embodiment, the anti-PACAP antibody contain a heavy chain comprising the following  
 sequence:  
 EVQLVESGGGLVQPGGSLRLSCAASGIDLSYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDNSK  
 20 NTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV  
 SWNSGALTSGVHTFPAVLQSSGLYSLSSVVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVL  
 HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG  
 QPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1604).  
 25

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1341 which consists of the light chain variable region of SEQ ID NO: 1342 linked to the light chain constant region of SEQ ID NO: 1350.  
 30

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:



DIQLTQSPSTLSASVGDRTITCQSSESVYGNLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISL  
QPDDFATYYCAGGDISEGVAFGGGTKVEIKR (SEQ ID NO: 1342).

- 5 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab10.H3, and that contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKAD  
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1350).

- 10 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1324; SEQ ID NO: 1326; and SEQ ID NO: 1328, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1321 or 1604, or which contain the variable heavy chain sequence of SEQ ID NO: 1322, and/or which further contain one, two, or three of the polypeptide  
15 sequences of SEQ ID NO: 1344; SEQ ID NO: 1346; and SEQ ID NO: 1348, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1341, or which contain the variable light chain sequence of SEQ ID NO: 1342, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding  
20 fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

- The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof  
25 comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1323; SEQ ID NO: 1325; SEQ ID NO: 1327; and SEQ ID NO: 1329, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1321 or 1604, or the variable heavy chain sequence of SEQ ID NO: 1322, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1343; SEQ ID NO: 1345; SEQ ID NO: 1347; and SEQ ID NO: 1349, which correspond to the FRs (constant regions) of  
30 the light chain sequence of SEQ ID NO: 1341, or the variable light chain sequence of SEQ ID NO: 1342, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least  
5 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1321, 1604, or SEQ ID NO: 1322, or polypeptides that are at least 90% or 95% identical thereto. In  
10 another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1341, or SEQ ID NO: 1342, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof  
15 having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1324; SEQ ID NO: 1326; and SEQ ID NO: 1328, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1321 or 1604, or the variable heavy chain sequence of SEQ ID NO: 1322, or sequences that are at least 90% or 95% identical thereto.

20 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1344; SEQ ID NO: 1346; and SEQ ID NO: 1348, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1341, or the variable  
25 light chain sequence of SEQ ID NO: 1342, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1323; SEQ ID NO: 1325; SEQ ID NO: 1327; and SEQ ID NO:  
30 1329, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1321 or 1604, or the variable heavy chain sequence of SEQ ID NO: 1322, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1343; SEQ ID NO: 1345; SEQ ID NO: 1347; and SEQ ID NO: 1349, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1341, or the variable light chain sequence of SEQ ID NO: 1342, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1322; the variable light chain region of SEQ ID NO: 1342; the complementarity determining regions (SEQ ID NO: 1324; SEQ ID NO: 1326; and SEQ ID NO: 1328) of the variable heavy chain region of SEQ ID NO: 1322; and the complementarity determining regions (SEQ ID NO: 1344; SEQ ID NO: 1346; and SEQ ID NO: 1348) of the variable light chain region of SEQ ID NO: 1342, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1322; the variable light chain region of SEQ ID NO: 1342; the framework regions (SEQ ID NO: 1323; SEQ ID NO: 1325; SEQ ID NO: 1327; and SEQ ID NO: 1329) of the variable heavy chain region of SEQ ID NO: 1322; and the framework regions (SEQ ID NO: 1343; SEQ ID NO: 1345; SEQ ID NO: 1347; and SEQ ID NO: 1349) of the variable light chain region of SEQ ID NO: 1342, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab10.H3, comprising, or alternatively consisting of, SEQ ID NO: 1321 or 1604 and SEQ ID NO: 1341, or SEQ ID NO: 1322 and SEQ ID NO: 1342, or an antibody or antigen-binding fragment comprising the CDRs of Ab10.H3 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab10.H3 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab10.H3, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab10.H3.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H3, the

Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1322 and the variable light chain sequence of SEQ ID NO: 1342, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1322 and/or SEQ ID NO: 1342 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H3. In another embodiment of the invention, anti-PACAP antibodies such as Ab10.H3 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab10.H3, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1322, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1342. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1342. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can

comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1341.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof  
5 according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies  
or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino  
acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1322  
and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ  
ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (b) a variable light chain  
10 comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity  
to SEQ ID NO: 1342 and comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence  
consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348. Alternatively, the  
anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy  
chain having the amino acid sequence of SEQ ID NO: 1322, and/or (b) a variable light chain having the  
15 amino acid sequence of SEQ ID NO: 1342. Alternatively, the anti-PACAP antibodies and/or antigen-  
binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of  
SEQ ID NO: 1322, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1342. In  
another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may  
comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98,  
20 or 99% sequence identity to SEQ ID NO: 1321 or 1604 and comprising a CDR1 sequence consisting of  
SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of  
SEQ ID NO: 1328; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90,  
95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1341 and comprising a CDR1 sequence  
consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence  
25 consisting of SEQ ID NO: 1348. Alternatively, the anti-PACAP antibodies and/or antigen-binding  
fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1321  
or 1604, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1341. Alternatively,  
the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain  
having the amino acid sequence of SEQ ID NO: 1321 or 1604, and (b) a light chain having the amino  
30 acid sequence of SEQ ID NO: 1341.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

- a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90,  
95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1322 and comprising a CDR1 sequence

- consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1342 and comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;
- 5 CDR3 sequence consisting of SEQ ID NO: 1348;
- b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1342;
- c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1342;
- 10 d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1321 or 1604 and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1341 and comprising a CDR1 sequence
- 15 consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;
- e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1341; and/or
- f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and (ii) a
- 20 light chain having the amino acid sequence of SEQ ID NO: 1341.

#### Antibody Ab10.H4

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of

25 SEQ ID NO: 1361 which consists of the heavy chain variable region of SEQ ID NO: 1362 linked to the heavy chain constant region of SEQ ID NO: 1370.

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the

30 sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSYYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDNISK  
NTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLVTVSS (SEQ ID NO: 1362).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab10.H4, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

5 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT  
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE  
VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF  
SCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO: 1370).

10

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1381 which consists of the light chain variable region of SEQ ID NO: 1382 linked to the light chain constant region of SEQ ID NO: 1390.

15

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

DIVLTQSPSTLSASVGDRTITCQSSSEVYGNYLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISLQ  
20 PDDFATYYCAGGDISEGVAFGGGTKVEIKR (SEQ ID NO: 1382).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab10.H4, and that contain a constant light chain sequence comprising the sequence set forth below:

25 TVAAPSVFIFPPSDEQLKSGTASVCLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKAD  
YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 1390).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of  
30 SEQ ID NO: 1364; SEQ ID NO: 1366; and SEQ ID NO: 1368, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1361, or which contain the variable heavy chain sequence of SEQ ID NO: 1362, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1384; SEQ ID NO: 1386; and SEQ ID NO: 1388, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1381, or which contain the variable

light chain sequence of SEQ ID NO: 1382, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified  
5 variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1363; SEQ ID NO:  
10 1365; SEQ ID NO: 1367; and SEQ ID NO: 1369, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1361, or the variable heavy chain sequence of SEQ ID NO: 1362, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1383; SEQ ID NO: 1385; SEQ ID NO: 1387; and SEQ ID NO: 1389, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1381, or the variable light chain sequence of SEQ ID NO: 1382, or  
15 combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or  
20 more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments  
25 thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1361, or SEQ ID NO: 1362, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1381, or SEQ ID NO: 1382, or polypeptides that are at least 90% or 95% identical thereto.  
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In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1364; SEQ ID NO: 1366; and SEQ ID NO: 1368, which correspond



to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1361, or the variable heavy chain sequence of SEQ ID NO: 1362, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof  
5 having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1384; SEQ ID NO: 1386; and SEQ ID NO: 1388, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1381, or the variable light chain sequence of SEQ ID NO: 1382, or sequences that are at least 90% or 95% identical thereto.

10 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1363; SEQ ID NO: 1365; SEQ ID NO: 1367; and SEQ ID NO: 1369, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1361, or the variable heavy chain sequence of SEQ ID NO: 1362, or sequences that are at least 90% or 95%  
15 identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1383; SEQ ID NO: 1385; SEQ ID NO: 1387; and SEQ  
20 ID NO: 1389, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1381, or the variable light chain sequence of SEQ ID NO: 1382, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that  
25 include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1362; the variable light chain region of SEQ ID NO: 1382; the complementarity determining regions (SEQ ID NO: 1364; SEQ ID NO: 1366; and SEQ ID NO: 1368)  
30 of the variable heavy chain region of SEQ ID NO: 1362; and the complementarity determining regions (SEQ ID NO: 1384; SEQ ID NO: 1386; and SEQ ID NO: 1388) of the variable light chain region of SEQ ID NO: 1382, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable

heavy chain region of SEQ ID NO: 1362; the variable light chain region of SEQ ID NO: 1382; the framework regions (SEQ ID NO: 1363; SEQ ID NO: 1365; SEQ ID NO: 1367; and SEQ ID NO: 1369) of the variable heavy chain region of SEQ ID NO: 1362; and the framework regions (SEQ ID NO: 1383; SEQ ID NO: 1385; SEQ ID NO: 1387; and SEQ ID NO: 1389) of the variable light chain region of SEQ ID NO: 1382, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab10.H4, comprising, or alternatively consisting of, SEQ ID NO: 1361 and SEQ ID NO: 1381, or SEQ ID NO: 1362 and SEQ ID NO: 1382, or an antibody or antigen-binding fragment comprising the CDRs of Ab10.H4 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab10.H4 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab10.H4, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab10.H4.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H4, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1362 and the variable light chain sequence of SEQ ID NO: 1382, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1362 and/or SEQ ID NO: 1382 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H4. In another embodiment of the invention, anti-PACAP antibodies such as Ab10.H4 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab10.H4, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 1364; a CDR2 sequence consisting of SEQ ID NO: 1366; and a CDR3 sequence consisting of SEQ ID NO: 1368; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1384; a CDR2 sequence consisting of SEQ ID NO: 1386; and a CDR3 sequence consisting of SEQ ID NO: 1388. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1362, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1382. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1362, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1382. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1361, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1381.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1362 and comprising a CDR1 sequence consisting of SEQ ID NO: 1364; a CDR2 sequence consisting of SEQ ID NO: 1366; and a CDR3 sequence consisting of SEQ ID NO: 1368; and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1382 and comprising a CDR1 sequence consisting of SEQ ID NO: 1384; a CDR2 sequence consisting of SEQ ID NO: 1386; and a CDR3 sequence consisting of SEQ ID NO: 1388. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1362, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1382. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1362, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1382. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98,

or 99% sequence identity to SEQ ID NO: 1361 and comprising a CDR1 sequence consisting of SEQ ID NO: 1364; a CDR2 sequence consisting of SEQ ID NO: 1366; and a CDR3 sequence consisting of SEQ ID NO: 1368; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1381 and comprising a CDR1 sequence consisting of

5 SEQ ID NO: 1384; a CDR2 sequence consisting of SEQ ID NO: 1386; and a CDR3 sequence consisting of SEQ ID NO: 1388. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1361, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1381. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid

10 sequence of SEQ ID NO: 1361, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1381.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90,

15 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1362 and comprising a CDR1 sequence consisting of SEQ ID NO: 1364; a CDR2 sequence consisting of SEQ ID NO: 1366; and a CDR3 sequence consisting of SEQ ID NO: 1368; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1382 and comprising a CDR1 sequence consisting of SEQ ID NO: 1384; a CDR2 sequence consisting of SEQ ID NO: 1386; and a

20 CDR3 sequence consisting of SEQ ID NO: 1388;

b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1362, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1382;

c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1362, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1382;

25 d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1361 and comprising a CDR1 sequence consisting of SEQ ID NO: 1364; a CDR2 sequence consisting of SEQ ID NO: 1366; and a CDR3 sequence consisting of SEQ ID NO: 1368; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1381 and comprising a CDR1 sequence consisting

30 of SEQ ID NO: 1384; a CDR2 sequence consisting of SEQ ID NO: 1386; and a CDR3 sequence consisting of SEQ ID NO: 1388;

e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1361, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1381; and/or

- f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1361, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 1381.

#### Antibody Ab10.H5

- 5 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 1401 which consists of the heavy chain variable region of SEQ ID NO: 1402 linked to the heavy chain constant region of SEQ ID NO: 1410.

- 10 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSYYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDNSKNTVY LQMNSLRAEDTAVYFCARDLDLWGQGTLVTVSS (SEQ ID NO: 1402).

15

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab10.H5, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

- 20 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1410).

25

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1421 which consists of the light chain variable region of SEQ ID NO: 1422 linked to the light chain constant region of SEQ ID NO: 1430.

30

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

QLTQSPSTLSASVGDRVITTCQSSSEVYGNYLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISLQPD  
DDFATYYCAGGDISEGVAFGGGTKVEIKR (SEQ ID NO: 1422).

- 5 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab10.H5, and that contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSLTLSKAD  
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1430).

- 10 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1404; SEQ ID NO: 1406; and SEQ ID NO: 1408, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1401, or which contain the variable heavy chain sequence of SEQ ID NO: 1402, and/or which further contain one, two, or three of the polypeptide  
15 sequences of SEQ ID NO: 1424; SEQ ID NO: 1426; and SEQ ID NO: 1428, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1421, or which contain the variable light chain sequence of SEQ ID NO: 1422, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding  
20 fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

- The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof  
25 comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1403; SEQ ID NO: 1405; SEQ ID NO: 1407; and SEQ ID NO: 1409, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1401, or the variable heavy chain sequence of SEQ ID NO: 1402, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1423; SEQ ID NO: 1425; SEQ ID NO: 1427; and SEQ ID NO: 1429, which correspond to the FRs (constant regions) of the light  
30 chain sequence of SEQ ID NO: 1421, or the variable light chain sequence of SEQ ID NO: 1422, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least  
5 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1401, or SEQ ID NO: 1402, or polypeptides that are at least 90% or 95% identical thereto. In another  
10 embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1421, or SEQ ID NO: 1422, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof  
15 having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1404; SEQ ID NO: 1406; and SEQ ID NO: 1408, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1401, or the variable heavy chain sequence of SEQ ID NO: 1402, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof  
20 having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1424; SEQ ID NO: 1426; and SEQ ID NO: 1428, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1421, or the variable light chain sequence of SEQ ID NO: 1422, or sequences that are at least 90% or 95% identical thereto.

25 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1403; SEQ ID NO: 1405; SEQ ID NO: 1407; and SEQ ID NO: 1409, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1401,  
30 or the variable heavy chain sequence of SEQ ID NO: 1402, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or

four of the polypeptide sequences of SEQ ID NO: 1423; SEQ ID NO: 1425; SEQ ID NO: 1427; and SEQ ID NO: 1429, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1421, or the variable light chain sequence of SEQ ID NO: 1422, or sequences that are at least 90% or 95% identical thereto.

5

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments:

10 the variable heavy chain region of SEQ ID NO: 1402; the variable light chain region of SEQ ID NO: 1422; the complementarity determining regions (SEQ ID NO: 1404; SEQ ID NO: 1406; and SEQ ID NO: 1408) of the variable heavy chain region of SEQ ID NO: 1402; and the complementarity determining regions (SEQ ID NO: 1424; SEQ ID NO: 1426; and SEQ ID NO: 1428) of the variable light chain region of SEQ ID NO: 1422, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the  
15 invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1402; the variable light chain region of SEQ ID NO: 1422; the framework regions (SEQ ID NO: 1403; SEQ ID NO: 1405; SEQ ID NO: 1407; and SEQ ID NO: 1409) of the variable heavy chain region of SEQ ID NO: 1402; and the framework regions (SEQ ID NO: 1423; SEQ ID  
20 NO: 1425; SEQ ID NO: 1427; and SEQ ID NO: 1429) of the variable light chain region of SEQ ID NO: 1422, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab10.H5, comprising, or alternatively consisting of, SEQ ID NO: 1401 and SEQ ID NO: 1421, or SEQ ID NO: 1402 and SEQ ID NO:  
25 1422, or an antibody or antigen-binding fragment comprising the CDRs of Ab10.H5 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab10.H5 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab10.H5, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab10.H5.

30

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H5, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1402 and the variable light chain sequence of SEQ ID NO: 1422, or sequences that are at least 90%, 95%, 96%, 97%,



98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1402 and/or SEQ ID NO: 1422 that retain the binding specificity for PACAP.

5 In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H5. In another embodiment of the invention, anti-PACAP antibodies such as Ab10.H5 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia*  
10 *pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab10.H5, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy  
15 chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies  
20 or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 1404; a CDR2 sequence consisting of SEQ ID NO: 1406; and a CDR3 sequence consisting of SEQ ID NO: 1408; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1424; a CDR2 sequence consisting of SEQ ID NO: 1426; and a CDR3 sequence consisting of SEQ ID NO: 1428. Alternatively, the anti-PACAP antibodies and/or antigen-binding  
25 fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1402, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1422. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence  
30 of SEQ ID NO: 1402, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1422. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1401, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1421.

- [92] In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1402 and comprising a CDR1 sequence consisting of SEQ ID NO: 1404; a CDR2 sequence consisting of SEQ ID NO: 1406; and a CDR3 sequence consisting of SEQ ID NO: 1408; and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1422 and comprising a CDR1 sequence consisting of SEQ ID NO: 1424; a CDR2 sequence consisting of SEQ ID NO: 1426; and a CDR3 sequence consisting of SEQ ID NO: 1428.
- Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1402, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1422. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1402, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1422. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1401 and comprising a CDR1 sequence consisting of SEQ ID NO: 1404; a CDR2 sequence consisting of SEQ ID NO: 1406; and a CDR3 sequence consisting of SEQ ID NO: 1408; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1421 and comprising a CDR1 sequence consisting of SEQ ID NO: 1424; a CDR2 sequence consisting of SEQ ID NO: 1426; and a CDR3 sequence consisting of SEQ ID NO: 1428. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1401, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1421.
- Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1401, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1421.

- In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises
- a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1402 and comprising a CDR1 sequence consisting of SEQ ID NO: 1404; a CDR2 sequence consisting of SEQ ID NO: 1406; and a CDR3 sequence consisting of SEQ ID NO: 1408; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1422 and comprising a

CDR1 sequence consisting of SEQ ID NO: 1424; a CDR2 sequence consisting of SEQ ID NO: 1426; and a CDR3 sequence consisting of SEQ ID NO: 1428;

- b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1402, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1422;
- 5 c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1402, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1422;
- d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1401 and comprising a CDR1 sequence consisting of SEQ ID NO: 1404; a CDR2 sequence consisting of SEQ ID NO: 1406; and a CDR3 sequence consisting of SEQ ID NO: 1408; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1421 and comprising a CDR1 sequence consisting of SEQ ID NO: 1424; a CDR2 sequence consisting of SEQ ID NO: 1426; and a CDR3 sequence consisting of SEQ ID NO: 1428;
- 10 e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1401, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1421; and/or
- 15 f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1401, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 1421.

#### **Antibody Ab10.H6**

- 20 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of SEQ ID NO: 1441 which consists of the heavy chain variable region of SEQ ID NO: 1442 linked to the heavy chain constant region of SEQ ID NO: 1450.

- 25 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSYYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDNISK  
NTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLLTVSS (SEQ ID NO: 1442).

30

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab10.H6, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT  
 QTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE  
 VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
 VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF  
 5 SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1450).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
 having binding specificity to PACAP that contain a light chain sequence comprising the sequence of  
 SEQ ID NO: 1461 which consists of the light chain variable region of SEQ ID NO: 1462 linked to the light  
 10 chain constant region of SEQ ID NO: 1470.

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
 having binding specificity to PACAP that contain a variable light chain sequence comprising the  
 sequence set forth below:  
 15 QVLTQSPSTLSASVGDRTITCQSSSESVYGNLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISLQ  
 PDDFATYYCAGGDISEGVAFGGGTKVEIKR (SEQ ID NO: 1462).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
 having binding specificity to PACAP, that bind the same epitope as Ab10.H6, and that contain a  
 20 constant light chain sequence comprising the sequence set forth below:  
 TVAAPSVFIFPPSDEQLKSGTASVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKAD  
 YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1470).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
 25 having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of  
 SEQ ID NO: 1444; SEQ ID NO: 1446; and SEQ ID NO: 1448, which correspond to the CDRs (hypervariable  
 regions) of the heavy chain sequence of SEQ ID NO: 1441, or which contain the variable heavy chain  
 sequence of SEQ ID NO: 1442, and/or which further contain one, two, or three of the polypeptide  
 sequences of SEQ ID NO: 1464; SEQ ID NO: 1466; and SEQ ID NO: 1468, which correspond to the CDRs  
 30 (hypervariable regions) of the light chain sequence of SEQ ID NO: 1461, or which contain the variable  
 light chain sequence of SEQ ID NO: 1462, or antibodies or antigen-binding fragments containing  
 combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical  
 thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding  
 fragments comprise, or alternatively consist of, combinations of one or more of the exemplified

variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1443; SEQ ID NO: 1445; SEQ ID NO: 1447; and SEQ ID NO: 1449, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1441, or the variable heavy chain sequence of SEQ ID NO: 1442, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1463; SEQ ID NO: 1465; SEQ ID NO: 1467; and SEQ ID NO: 1469, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1461, or the variable light chain sequence of SEQ ID NO: 1462, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1441, or SEQ ID NO: 1442, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1461, or SEQ ID NO: 1462, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1444; SEQ ID NO: 1446; and SEQ ID NO: 1448, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1441, or the variable heavy chain sequence of SEQ ID NO: 1442, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the

polypeptide sequences of SEQ ID NO: 1464; SEQ ID NO: 1466; and SEQ ID NO: 1468, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1461, or the variable light chain sequence of SEQ ID NO: 1462, or sequences that are at least 90% or 95% identical thereto.

5 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1443; SEQ ID NO: 1445; SEQ ID NO: 1447; and SEQ ID NO: 1449, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1441, or the variable heavy chain sequence of SEQ ID NO: 1442, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1463; SEQ ID NO: 1465; SEQ ID NO: 1467; and SEQ ID NO: 1469, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1461, or the variable light chain sequence of SEQ ID NO: 1462, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1442; the variable light chain region of SEQ ID NO: 1462; the complementarity determining regions (SEQ ID NO: 1444; SEQ ID NO: 1446; and SEQ ID NO: 1448) of the variable heavy chain region of SEQ ID NO: 1442; and the complementarity determining regions (SEQ ID NO: 1464; SEQ ID NO: 1466; and SEQ ID NO: 1468) of the variable light chain region of SEQ ID NO: 1462, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1442; the variable light chain region of SEQ ID NO: 1462; the framework regions (SEQ ID NO: 1443; SEQ ID NO: 1445; SEQ ID NO: 1447; and SEQ ID NO: 1449) of the variable heavy chain region of SEQ ID NO: 1442; and the framework regions (SEQ ID NO: 1463; SEQ ID NO: 1465; SEQ ID NO: 1467; and SEQ ID NO: 1469) of the variable light chain region of SEQ ID NO: 1462, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab10.H6, comprising, or alternatively consisting of, SEQ ID NO: 1441 and SEQ ID NO: 1461, or SEQ ID NO: 1442 and SEQ ID NO: 1462, or an antibody or antigen-binding fragment comprising the CDRs of Ab10.H6 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab10.H6 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab10.H6, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab10.H6.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H6, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1442 and the variable light chain sequence of SEQ ID NO: 1462, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1442 and/or SEQ ID NO: 1462 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H6. In another embodiment of the invention, anti-PACAP antibodies such as Ab10.H6 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab10.H6, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 1444; a CDR2 sequence consisting of SEQ ID NO: 1446; and a CDR3

sequence consisting of SEQ ID NO: 1448; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1464; a CDR2 sequence consisting of SEQ ID NO: 1466; and a CDR3 sequence consisting of SEQ ID NO: 1468. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1442, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1462. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1442, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1462. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1441, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1461.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1442 and comprising a CDR1 sequence consisting of SEQ ID NO: 1444; a CDR2 sequence consisting of SEQ ID NO: 1446; and a CDR3 sequence consisting of SEQ ID NO: 1448; and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1462 and comprising a CDR1 sequence consisting of SEQ ID NO: 1464; a CDR2 sequence consisting of SEQ ID NO: 1466; and a CDR3 sequence consisting of SEQ ID NO: 1468. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1442, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1462. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1442, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1462. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1441 and comprising a CDR1 sequence consisting of SEQ ID NO: 1444; a CDR2 sequence consisting of SEQ ID NO: 1446; and a CDR3 sequence consisting of SEQ ID NO: 1448; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1461 and comprising a CDR1 sequence consisting of SEQ ID NO: 1464; a CDR2 sequence consisting of SEQ ID NO: 1466; and a CDR3 sequence consisting of



SEQ ID NO: 1468. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1441, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1461. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1441, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1461.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

- a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1442 and comprising a CDR1 sequence consisting of SEQ ID NO: 1444; a CDR2 sequence consisting of SEQ ID NO: 1446; and a CDR3 sequence consisting of SEQ ID NO: 1448; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1462 and comprising a CDR1 sequence consisting of SEQ ID NO: 1464; a CDR2 sequence consisting of SEQ ID NO: 1466; and a CDR3 sequence consisting of SEQ ID NO: 1468;
- b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1442, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1462;
- c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1442, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1462;
- d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1441 and comprising a CDR1 sequence consisting of SEQ ID NO: 1444; a CDR2 sequence consisting of SEQ ID NO: 1446; and a CDR3 sequence consisting of SEQ ID NO: 1448; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1461 and comprising a CDR1 sequence consisting of SEQ ID NO: 1464; a CDR2 sequence consisting of SEQ ID NO: 1466; and a CDR3 sequence consisting of SEQ ID NO: 1468;
- e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1441, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1461; and/or
- f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1441, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 1461.

#### **Antibody Ab21.H2**

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of

SEQ ID NO: 1481 which consists of the heavy chain variable region of SEQ ID NO: 1482 linked to the heavy chain constant region of SEQ ID NO: 1490.

- 5 In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSSYYMTWVRQAPGKGLEWIGFIDAGGSAYYATWAKGRFTISRDNSKNTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLVTVSS (SEQ ID NO: 1482).

- 10 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab21.H2, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT  
 15 QTYICNVNHKPSNTKVDKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHQKSLSLSPGK (SEQ ID NO: 1490).

- 20 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1501 which consists of the light chain variable region of SEQ ID NO: 1502 linked to the light chain constant region of SEQ ID NO: 1510.

- 25 In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

AVLTQSPSTLSASVGDRTITCKSSESVYGDYLAWFQQKPGKAPKQLIYDASTLASGVPSRFSGSGSGTEFTLTISLQ  
 PDDFATYYCAGGYVSAGVAFGGGKVEIKR (SEQ ID NO: 1502).

30

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab21.H2, and that contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD  
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1510).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof  
5 having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of  
SEQ ID NO: 1484; SEQ ID NO: 1486; and SEQ ID NO: 1488, which correspond to the CDRs (hypervariable  
regions) of the heavy chain sequence of SEQ ID NO: 1481, or which contain the variable heavy chain  
sequence of SEQ ID NO: 1482, and/or which further contain one, two, or three of the polypeptide  
sequences of SEQ ID NO: 1504; SEQ ID NO: 1506; and SEQ ID NO: 1508, which correspond to the CDRs  
10 (hypervariable regions) of the light chain sequence of SEQ ID NO: 1501, or which contain the variable  
light chain sequence of SEQ ID NO: 1502, or antibodies or antigen-binding fragments containing  
combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical  
thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding  
fragments comprise, or alternatively consist of, combinations of one or more of the exemplified  
15 variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences  
set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof  
comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1483; SEQ ID NO:  
20 1485; SEQ ID NO: 1487; and SEQ ID NO: 1489, which correspond to the FRs (constant regions) of the  
heavy chain sequence of SEQ ID NO: 1481, or the variable heavy chain sequence of SEQ ID NO: 1482,  
and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1503; SEQ ID NO: 1505;  
SEQ ID NO: 1507; and SEQ ID NO: 1509, which correspond to the FRs (constant regions) of the light  
chain sequence of SEQ ID NO: 1501, or the variable light chain sequence of SEQ ID NO: 1502, or  
25 combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%,  
97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments  
thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or  
30 more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy  
chain and light chain sequences set forth above, including all of them, or sequences that are at least  
90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1481, or SEQ ID NO: 1482, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1501, or SEQ ID NO: 1502, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1484; SEQ ID NO: 1486; and SEQ ID NO: 1488, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1481, or the variable heavy chain sequence of SEQ ID NO: 1482, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1504; SEQ ID NO: 1506; and SEQ ID NO: 1508, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1501, or the variable light chain sequence of SEQ ID NO: 1502, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1483; SEQ ID NO: 1485; SEQ ID NO: 1487; and SEQ ID NO: 1489, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1481, or the variable heavy chain sequence of SEQ ID NO: 1482, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1503; SEQ ID NO: 1505; SEQ ID NO: 1507; and SEQ ID NO: 1509, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1501, or the variable light chain sequence of SEQ ID NO: 1502, or sequences that are at least 90% or 95% identical thereto.

The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments:

5 the variable heavy chain region of SEQ ID NO: 1482; the variable light chain region of SEQ ID NO: 1502; the complementarity determining regions (SEQ ID NO: 1484; SEQ ID NO: 1486; and SEQ ID NO: 1488) of the variable heavy chain region of SEQ ID NO: 1482; and the complementarity determining regions (SEQ ID NO: 1504; SEQ ID NO: 1506; and SEQ ID NO: 1508) of the variable light chain region of SEQ ID NO: 1502, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the

10 invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1482; the variable light chain region of SEQ ID NO: 1502; the framework regions (SEQ ID NO: 1483; SEQ ID NO: 1485; SEQ ID NO: 1487; and SEQ ID NO: 1489) of the variable heavy chain region of SEQ ID NO: 1482; and the framework regions (SEQ ID NO: 1503; SEQ ID

15 NO: 1505; SEQ ID NO: 1507; and SEQ ID NO: 1509) of the variable light chain region of SEQ ID NO: 1502, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab21.H2, comprising, or alternatively consisting of, SEQ ID NO: 1481 and SEQ ID NO: 1501, or SEQ ID NO: 1482 and SEQ ID NO:

20 1502, or an antibody or antigen-binding fragment comprising the CDRs of Ab21.H2 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab21.H2 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab21.H2, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab21.H2.

25

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H2, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1482 and the variable light chain sequence of SEQ ID NO: 1502, or sequences that are at least 90%, 95%, 96%, 97%,

30 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1482 and/or SEQ ID NO: 1502 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab21.H2. In another embodiment of the invention, anti-PACAP antibodies such as Ab21.H2 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab21.H2, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 1484; a CDR2 sequence consisting of SEQ ID NO: 1486; and a CDR3 sequence consisting of SEQ ID NO: 1488; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1504; a CDR2 sequence consisting of SEQ ID NO: 1506; and a CDR3 sequence consisting of SEQ ID NO: 1508. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1482, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1502. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1482, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1502. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1481, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1501.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1482

- and comprising a CDR1 sequence consisting of SEQ ID NO: 1484; a CDR2 sequence consisting of SEQ ID NO: 1486; and a CDR3 sequence consisting of SEQ ID NO: 1488; and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1502 and comprising a CDR1 sequence consisting of SEQ ID NO: 1504; a CDR2 sequence
- 5 consisting of SEQ ID NO: 1506; and a CDR3 sequence consisting of SEQ ID NO: 1508. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1482, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1502. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of
- 10 SEQ ID NO: 1482, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1502. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1481 and comprising a CDR1 sequence consisting of SEQ ID NO: 1484; a CDR2 sequence consisting of SEQ ID NO: 1486; and a CDR3 sequence consisting of SEQ ID
- 15 NO: 1488; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1501 and comprising a CDR1 sequence consisting of SEQ ID NO: 1504; a CDR2 sequence consisting of SEQ ID NO: 1506; and a CDR3 sequence consisting of SEQ ID NO: 1508. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1481, and/or (b) a light
- 20 chain having the amino acid sequence of SEQ ID NO: 1501. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1481, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1501.
- 25 In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises
- a. a variable heavy chain comprising the CDR1 sequence consisting of SEQ ID NO: 1484; a CDR2 sequence consisting of SEQ ID NO: 1486; and a CDR3 sequence consisting of SEQ ID NO: 1488; and/or
- b. a variable light chain comprising the CDR1 sequence consisting of SEQ ID NO: 1504; a
- 30 CDR2 sequence consisting of SEQ ID NO: 1506; and a CDR3 sequence consisting of SEQ ID NO: 1508, wherein optionally said antibody comprises:
- (a) (i) the variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1482, and/or (ii) the variable light chain

comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1502;

- (b) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1482, or (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 1502;
- 5 (c) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1482, and (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 1502;
- (d) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1481, and/or (ii) the light chain having the amino acid sequence of SEQ ID NO: 1501; or
- (e) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1481, and (ii) the light
- 10 chain having the amino acid sequence of SEQ ID NO: 1501.

### **Antibody Ab21.H3**

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of

15 SEQ ID NO: 1521 which consists of the heavy chain variable region of SEQ ID NO: 1522 linked to the heavy chain constant region of SEQ ID NO: 1530.

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the

20 sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSSYYMTWVRQAPGKGLEWIGFIDAGGSAYYATWAKGRFTISRDNK  
NTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLVTVSS (SEQ ID NO: 1522).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab21.H3, and that contain a

25 constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT  
QTYICNVNHKPSNTKVDKKVEPKSCDKHTCTPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE  
30 VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF  
SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1530).



In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1541 which consists of the light chain variable region of SEQ ID NO: 1542 linked to the light chain constant region of SEQ ID NO: 1550.

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In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

DIQLTQSPSTLSASVGDRTITCKSSESVYGDYLAWFQQKPGKAPKQLIYDASTLASGVPSRFSGSGSGTEFTLTSSL

10 QPDDFATYYCAGGYVSAGVAFGGGKVEIKR (SEQ ID NO: 1542).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab21.H3, and that contain a constant light chain sequence comprising the sequence set forth below:

15 TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKAD  
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1550).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1524; SEQ ID NO: 1526; and SEQ ID NO: 1528, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1521, or which contain the variable heavy chain sequence of SEQ ID NO: 1522, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1544; SEQ ID NO: 1546; and SEQ ID NO: 1548, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1541, or which contain the variable light chain sequence of SEQ ID NO: 1542, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1523; SEQ ID NO: 1525; SEQ ID NO: 1527; and SEQ ID NO: 1529, which correspond to the FRs (constant regions) of the

heavy chain sequence of SEQ ID NO: 1521, or the variable heavy chain sequence of SEQ ID NO: 1522, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1543; SEQ ID NO: 1545; SEQ ID NO: 1547; and SEQ ID NO: 1549, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1541, or the variable light chain sequence of SEQ ID NO: 1542, or combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1521, or SEQ ID NO: 1522, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1541, or SEQ ID NO: 1542, or polypeptides that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1524; SEQ ID NO: 1526; and SEQ ID NO: 1528, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1521, or the variable heavy chain sequence of SEQ ID NO: 1522, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1544; SEQ ID NO: 1546; and SEQ ID NO: 1548, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1541, or the variable light chain sequence of SEQ ID NO: 1542, or sequences that are at least 90% or 95% identical thereto.

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of

the polypeptide sequences of SEQ ID NO: 1523; SEQ ID NO: 1525; SEQ ID NO: 1527; and SEQ ID NO: 1529, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1521, or the variable heavy chain sequence of SEQ ID NO: 1522, or sequences that are at least 90% or 95% identical thereto.

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In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1543; SEQ ID NO: 1545; SEQ ID NO: 1547; and SEQ ID NO: 1549, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1541, or the variable light chain sequence of SEQ ID NO: 1542, or sequences that are at least 90% or 95% identical thereto.

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The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1522; the variable light chain region of SEQ ID NO: 1542; the complementarity determining regions (SEQ ID NO: 1524; SEQ ID NO: 1526; and SEQ ID NO: 1528) of the variable heavy chain region of SEQ ID NO: 1522; and the complementarity determining regions (SEQ ID NO: 1544; SEQ ID NO: 1546; and SEQ ID NO: 1548) of the variable light chain region of SEQ ID NO: 1542, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1522; the variable light chain region of SEQ ID NO: 1542; the framework regions (SEQ ID NO: 1523; SEQ ID NO: 1525; SEQ ID NO: 1527; and SEQ ID NO: 1529) of the variable heavy chain region of SEQ ID NO: 1522; and the framework regions (SEQ ID NO: 1543; SEQ ID NO: 1545; SEQ ID NO: 1547; and SEQ ID NO: 1549) of the variable light chain region of SEQ ID NO: 1542, or sequences that are at least 90% or 95% identical thereto.

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In another embodiment of the invention, the anti-PACAP antibody is Ab21.H3, comprising, or alternatively consisting of, SEQ ID NO: 1521 and SEQ ID NO: 1541, or SEQ ID NO: 1522 and SEQ ID NO: 1542, or an antibody or antigen-binding fragment comprising the CDRs of Ab21.H3 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab21.H3 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%,

98%, or 99% identical to that of Ab21.H3, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab21.H3.

5 In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H3, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1522 and the variable light chain sequence of SEQ ID NO: 1542, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1522 and/or SEQ ID NO: 1542 that retain the binding  
10 specificity for PACAP.

In one embodiment described herein, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab21.H3. In another embodiment of the invention, anti-PACAP antibodies such as Ab21.H3 and Fab fragments may be produced via expression in mammalian cells, such as CHO, NSO, or HEK 293  
15 cells, fungal, insect, or microbial systems, such as yeast cells (for example haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody  
20 polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab21.H3, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

25 In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO: 1524; a CDR2 sequence consisting of SEQ ID NO: 1526; and a CDR3 sequence consisting of SEQ ID NO: 1528; and/or (b) a variable light chain comprising a CDR1 sequence  
30 consisting of SEQ ID NO: 1544; a CDR2 sequence consisting of SEQ ID NO: 1546; and a CDR3 sequence consisting of SEQ ID NO: 1548. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1522, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence

identity to SEQ ID NO: 1542. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1522, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1542. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can  
5 comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1521, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1541.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies  
10 or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1522 and comprising a CDR1 sequence consisting of SEQ ID NO: 1524; a CDR2 sequence consisting of SEQ ID NO: 1526; and a CDR3 sequence consisting of SEQ ID NO: 1528; and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity  
15 to SEQ ID NO: 1542 and comprising a CDR1 sequence consisting of SEQ ID NO: 1544; a CDR2 sequence consisting of SEQ ID NO: 1546; and a CDR3 sequence consisting of SEQ ID NO: 1548. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1522, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1542. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of  
20 SEQ ID NO: 1522, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1542. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1521 and comprising a CDR1 sequence consisting of SEQ ID  
25 NO: 1524; a CDR2 sequence consisting of SEQ ID NO: 1526; and a CDR3 sequence consisting of SEQ ID NO: 1528; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1541 and comprising a CDR1 sequence consisting of SEQ ID NO: 1544; a CDR2 sequence consisting of SEQ ID NO: 1546; and a CDR3 sequence consisting of SEQ ID NO: 1548. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof  
30 can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1521, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1541. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1521, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1541.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

- a. a variable heavy chain comprising the CDR1 sequence consisting of SEQ ID NO: 1524; a CDR2 sequence consisting of SEQ ID NO: 1526; and a CDR3 sequence consisting of SEQ ID NO: 1528;
- 5 and/or
- b. a variable light chain comprising the CDR1 sequence consisting of SEQ ID NO: 1544; a CDR2 sequence consisting of SEQ ID NO: 1546; and a CDR3 sequence consisting of SEQ ID NO: 1548, wherein optionally said antibody comprises:
  - (a) (i) the variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1522, and/or (ii) the variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1542;
  - (b) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1522, or (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 1542;
  - 15 (c) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1522, and (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 1542;
  - (d) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1521, and/or (ii) the light chain having the amino acid sequence of SEQ ID NO: 1541; or
  - (e) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1521, and (ii) the light chain having the amino acid sequence of SEQ ID NO: 1541.
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#### **Antibody Ab21.H4**

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that possess a heavy chain sequence comprising the sequence of  
 25 SEQ ID NO: 1561 which consists of the heavy chain variable region of SEQ ID NO: 1562 linked to the heavy chain constant region of SEQ ID NO: 1570.

In one embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable heavy chain sequence comprising the  
 30 sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSSYYMTWVRQAPGKGLEWIGFIDAGGSAYYATWAKGRFTISRDNK  
 NTVYQLQMNSLRAEDTAVYFCARDLDLWGQGTLLTVSS (SEQ ID NO: 1562).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that bind the same epitope as Ab21.H4, and that contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 1244, 1245, or 1246, or comprising the sequence set forth below:

5   ASTKGPSVFPLAPSSKSTSGGTAALGLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT  
 QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE  
 VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ  
 VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF  
 SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1570).

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In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a light chain sequence comprising the sequence of SEQ ID NO: 1581 which consists of the light chain variable region of SEQ ID NO: 1582 linked to the light chain constant region of SEQ ID NO: 1590.

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In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain a variable light chain sequence comprising the sequence set forth below:

DIVLTQSPSTLSASVGDRVTITCKSSESVYGDYLAWFQKPKGKAPKQLIYDASTLASGVPSRFSGSGSGTEFTLTISL  
 20   QPDDFATYYCAGGYVSAGVAFGGGKVEIKR (SEQ ID NO: 1582).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP, that bind the same epitope as Ab21.H4, and that contain a constant light chain sequence comprising the sequence set forth below:

25   TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKAD  
 YEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 1590).

In another embodiment, the invention includes antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP that contain one, two, or three of the polypeptide sequences of  
 30   SEQ ID NO: 1564; SEQ ID NO: 1566; and SEQ ID NO: 1568, which correspond to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1561, or which contain the variable heavy chain sequence of SEQ ID NO: 1562, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 1584; SEQ ID NO: 1586; and SEQ ID NO: 1588, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1581, or which contain the variable

light chain sequence of SEQ ID NO: 1582, or antibodies or antigen-binding fragments containing combinations of sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention and antigen-binding fragments comprise, or alternatively consist of, combinations of one or more of the exemplified  
5 variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

The invention further contemplates anti-PACAP antibodies and/or antigen-binding fragments thereof comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1563; SEQ ID NO:  
10 1565; SEQ ID NO: 1567; and SEQ ID NO: 1569, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1561, or the variable heavy chain sequence of SEQ ID NO: 1562, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1583; SEQ ID NO: 1585; SEQ ID NO: 1587; and SEQ ID NO: 1589, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1581, or the variable light chain sequence of SEQ ID NO: 1582, or  
15 combinations of these polypeptide sequences, or sequences that are at least 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical therewith.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments thereof of the invention or fragments comprise, or alternatively consist of, combinations of one or  
20 more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibodies and/or antigen-binding fragments  
25 thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1561, or SEQ ID NO: 1562, or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibodies and/or antigen-binding fragments thereof of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1581, or SEQ ID NO: 1582, or polypeptides that are at least 90% or 95% identical thereto.  
30

In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1564; SEQ ID NO: 1566; and SEQ ID NO: 1568, which correspond



to the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1561, or the variable heavy chain sequence of SEQ ID NO: 1562, or sequences that are at least 90% or 95% identical thereto.

5 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, or three of the polypeptide sequences of SEQ ID NO: 1584; SEQ ID NO: 1586; and SEQ ID NO: 1588, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1581, or the variable light chain sequence of SEQ ID NO: 1582, or sequences that are at least 90% or 95% identical thereto.

10 In a further embodiment of the invention, the antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1563; SEQ ID NO: 1565; SEQ ID NO: 1567; and SEQ ID NO: 1569, which correspond to the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1561, or the variable heavy chain sequence of SEQ ID NO: 1562, or sequences that are at least 90% or 95% identical thereto.

15 In a further embodiment of the invention, the subject antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 1583; SEQ ID NO: 1585; SEQ ID NO: 1587; and SEQ ID NO: 1589, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1581, or the variable light chain sequence of SEQ ID NO: 1582, or sequences that are at least 90% or 95% identical thereto.

25 The invention also contemplates anti-PACAP antibodies and/or antigen-binding fragments that include one or more of the antibody fragments described herein. In one embodiment, antibodies and/or antigen-binding fragments thereof having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 1562; the variable light chain region of SEQ ID NO: 1582; the complementarity determining regions (SEQ ID NO: 1564; SEQ ID NO: 1566; and SEQ ID NO: 1568) of the variable heavy chain region of SEQ ID NO: 1562; and the complementarity determining regions (SEQ ID NO: 1584; SEQ ID NO: 1586; and SEQ ID NO: 1588) of the variable light chain region of SEQ ID NO: 1582, or sequences that are at least 90% or 95% identical thereto. In another embodiment of the invention, fragments of the antibodies having binding specificity to PACAP comprise, or alternatively consist of, one, two, three, or more, including all of the following antibody fragments: the variable

heavy chain region of SEQ ID NO: 1562; the variable light chain region of SEQ ID NO: 1582; the framework regions (SEQ ID NO: 1563; SEQ ID NO: 1565; SEQ ID NO: 1567; and SEQ ID NO: 1569) of the variable heavy chain region of SEQ ID NO: 1562; and the framework regions (SEQ ID NO: 1583; SEQ ID NO: 1585; SEQ ID NO: 1587; and SEQ ID NO: 1589) of the variable light chain region of SEQ ID NO: 1582, or sequences that are at least 90% or 95% identical thereto.

In another embodiment of the invention, the anti-PACAP antibody is Ab21.H4, comprising, or alternatively consisting of, SEQ ID NO: 1561 and SEQ ID NO: 1581, or SEQ ID NO: 1562 and SEQ ID NO: 1582, or an antibody or antigen-binding fragment comprising the CDRs of Ab21.H4 and having at least one of the biological activities set forth herein, or is an anti-PACAP antibody that competes with Ab21.H4 in binding PACAP, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical to that of Ab21.H4, or an antibody that binds to the same or overlapping epitope(s) on PACAP as Ab21.H4.

In a further embodiment of the invention, antigen-binding fragments comprise, or alternatively consist of, Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H4, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 1562 and the variable light chain sequence of SEQ ID NO: 1582, or sequences that are at least 90%, 95%, 96%, 97%, 98%, or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 1562 and/or SEQ ID NO: 1582 that retain the binding specificity for PACAP.

In one embodiment, Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab21.H4. In another embodiment of the invention, anti-PACAP antibodies such as Ab21.H4 and Fab fragments 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 haploid or diploid yeast, such as haploid or diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP, including the heavy and/or light chains of Ab21.H4, as well as fragments, variants, and combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them, or sequences that are at least 90% or 95% identical thereto.

In a specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising a CDR1  
5 sequence consisting of SEQ ID NO: 1564; a CDR2 sequence consisting of SEQ ID NO: 1566; and a CDR3 sequence consisting of SEQ ID NO: 1568; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO: 1584; a CDR2 sequence consisting of SEQ ID NO: 1586; and a CDR3 sequence consisting of SEQ ID NO: 1588. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain comprising an amino acid sequence with at  
10 least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1562, and/or (b) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1582. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1562, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:  
15 1582. More specifically, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1561, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1581.

In another specific embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof  
20 according to the invention, are preferably human, humanized, or chimerized anti-PACAP antibodies or antigen-binding fragments thereof, and comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1562 and comprising a CDR1 sequence consisting of SEQ ID NO: 1564; a CDR2 sequence consisting of SEQ ID NO: 1566; and a CDR3 sequence consisting of SEQ ID NO: 1568; and/or (b) a variable light chain  
25 comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1582 and comprising a CDR1 sequence consisting of SEQ ID NO: 1584; a CDR2 sequence consisting of SEQ ID NO: 1586; and a CDR3 sequence consisting of SEQ ID NO: 1588. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1562, and/or (b) a variable light chain having the  
30 amino acid sequence of SEQ ID NO: 1582. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1562, and (b) a variable light chain having the amino acid sequence of SEQ ID NO: 1582. In another embodiment, the anti-PACAP antibodies and/or antigen-binding fragments thereof may comprise (a) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98,

or 99% sequence identity to SEQ ID NO: 1561 and comprising a CDR1 sequence consisting of SEQ ID NO: 1564; a CDR2 sequence consisting of SEQ ID NO: 1566; and a CDR3 sequence consisting of SEQ ID NO: 1568; and/or (b) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1581 and comprising a CDR1 sequence consisting of

5 SEQ ID NO: 1584; a CDR2 sequence consisting of SEQ ID NO: 1586; and a CDR3 sequence consisting of SEQ ID NO: 1588. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO: 1561, and/or (b) a light chain having the amino acid sequence of SEQ ID NO: 1581. Alternatively, the anti-PACAP antibodies and/or antigen-binding fragments thereof can comprise (a) a heavy chain having the amino acid

10 sequence of SEQ ID NO: 1561, and (b) a light chain having the amino acid sequence of SEQ ID NO: 1581.

In another embodiment, the invention contemplates an isolated anti-PACAP antibody comprising a V<sub>H</sub> polypeptide sequence selected from: SEQ ID NO: 962; SEQ ID NO: 1282; SEQ ID NO: 1322; SEQ ID NO: 1362; SEQ ID NO: 1402; SEQ ID NO: 1442; SEQ ID NO: 842; SEQ ID NO: 1202; SEQ ID NO: 1482; SEQ ID NO: 1522; SEQ ID NO: 1562; SEQ ID NO: 882; SEQ ID NO: 922, or a variant thereof; and further comprising a V<sub>L</sub> polypeptide sequence selected from: SEQ ID NO: 982; SEQ ID NO: 1302; SEQ ID NO: 1342; SEQ ID NO: 1382; SEQ ID NO: 1422; SEQ ID NO: 1462; SEQ ID NO: 862; SEQ ID NO: 1222; SEQ ID NO: 1502; SEQ ID NO: 1542; SEQ ID NO: 1582; SEQ ID NO: 902; SEQ ID NO: 942, or a variant thereof,

20 wherein one or more of the framework region residues ("FR residues") and/or CDR residues in said V<sub>H</sub> or V<sub>L</sub> polypeptide has been substituted with another amino acid residue resulting in an anti-PACAP antibody that specifically binds PACAP.

In one embodiment, the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

25 a. a variable heavy chain comprising the CDR1 sequence consisting of SEQ ID NO: 1564; a CDR2 sequence consisting of SEQ ID NO: 1566; and a CDR3 sequence consisting of SEQ ID NO: 1568; and/or

b. a variable light chain comprising the CDR1 sequence consisting of SEQ ID NO: 1584; a CDR2 sequence consisting of SEQ ID NO: 1586; and a CDR3 sequence consisting of SEQ ID NO: 1588,

30 wherein optionally said antibody comprises:

(a) (i) the variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1562, and/or (ii) the variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1582;

- (b) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1562, or (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 1582;
- (c) (i) the variable heavy chain having the amino acid sequence of SEQ ID NO: 1562, and (ii) the variable light chain having the amino acid sequence of SEQ ID NO: 1582;
- 5 (d) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1561, and/or (ii) the light chain having the amino acid sequence of SEQ ID NO: 1581; or
- (e) (i) the heavy chain having the amino acid sequence of SEQ ID NO: 1561, and (ii) the light chain having the amino acid sequence of SEQ ID NO: 1581.

#### 10 **Exemplary Polynucleotides Encoding Anti-PACAP Antibody Polypeptides**

The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP.

The invention further contemplates host cells and vectors comprising said polynucleotides.

15

The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual CDRs (hypervariable regions), as set forth herein, as well as host cells comprising said vector sequences. In embodiments of the invention, the host cells are mammalian cells, such as CHO cells. In embodiments of the invention, the host cells are yeast cells, such as yeast cells of the genus *Pichia*.

20

#### **Antibody Ab10.H**

In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 971 which encodes the heavy chain sequence of SEQ ID NO: 961 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 972 and the heavy chain constant region coding sequence of SEQ ID NO: 980.

25

- 30 In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 962:

gaggtgcagcttgaggagctgggggaggctgtccagcctggggggtccctgagactctcctgtgcagcctctggaatcgacctcaatagcta  
ctacatgacctgggtccgtcaggctccagggaagggtgaggatcgattcattgatctggtggtgacgcatactacgcgagctgggcg

aaaggccgattcacatctccagagacaattccaagaacaccgtgtatcttcaaataaacagcctgagagctgaggacactgctgtgtattctg  
tgctagagatcttgacttgtggggccaaggacccctcgtcaccgtctcgagc (SEQ ID NO: 972).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
5 consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide  
sequence of SEQ ID NO: 970:

gcctccaccaagggcccatcggcttccccctggcaccctcctccaagagcacctctgggggcacagcgccctgggctgctgtgtaaggacta  
cttccccgaacgggtgacgggtgctggaactcaggcgccctgaccagcggtgcacacctccgggtgtctacagtcctcaggactctactc  
cctcagcagcgtggtagcgtgcccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaagggtgga  
10 caagaaagttgagcccaaatcttgtagaaaaactcacacatgcccaccgtgccagcacctgaactcctggggggaccgtcagttcttcttcc  
ccccaaaacccaaggacaccctcatgatctccggaccctgagggtcacatgctgtggtgggagctgagccacgaagaccctgaggtaagtt  
caactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgaggagagcagtagccagcacgtaccgtgtggtcagcgtctc  
caccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctc  
caaagccaaaggcgagccccgagaaccacaggtgtacacctgcccccatccgggaggagatgaccaagaaccaggtcagcctgacctgcc  
15 tggtaaaaggcttctatcccagcgacatgccgtggagtgaggagacaaatgggcagccggagagaactacaagaccacgcctcccgtgctgg  
actccgacggctcttcttctctacagcaagctcaccgtggacaagagcaggtggcagggggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 980).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the  
20 polynucleotide sequence of SEQ ID NO: 991 which encodes the light chain polypeptide sequence of  
SEQ ID NO: 981 and which consists of the light chain variable region coding sequence of SEQ ID NO:  
992 and the light chain constant region coding sequence of SEQ ID NO: 1000.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
25 consist of, the following polynucleotide sequence encoding the variable light chain polypeptide  
sequence of SEQ ID NO: 982:

gacgcccagctgacccagtcctctccaccctgtctgcatctgtaggagacagagtcacatcacttgctcagtcagtgagagtggttacggtaac  
tacttagcctgggttcagcagaaaccaggaaaagccctaagttcctgatctatgaagcatccaaactggaatctggagtcctcatcaagggtcag  
cggcagtggtatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaactactactgtgcaggcggtgatattagtg  
30 aggtgtgtcttccggcgaggaaaccaaggtggaaatcaaacgt (SEQ ID NO: 992).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
consist of, the following polynucleotide sequence encoding the constant light chain polypeptide  
sequence of SEQ ID NO: 990:

acggtagcggcccatctgtcttcatcttccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcc  
cagagaggccaaagtacagtggagggtggataacgccctccaatcgggtaactcccaggagagtgacagagcaggacagcaaggacagc  
acctacagcctcagcagcaccctgacgtgagcaagcagactacgagaaacaaaagtctacgcctgcgaagtcacccatcagggcctgagc  
tcgccgtcacaagagcttcaacaggggagagtgt (SEQ ID NO: 1000).

5

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 974; SEQ ID NO: 976; and SEQ ID NO: 978, which correspond to polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 961, or the variable heavy chain sequence of SEQ ID NO: 962, and/or one or more of the polynucleotide sequences of SEQ ID NO: 994; SEQ ID NO: 996; and SEQ ID NO: 998, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 981, or the variable light chain sequence of SEQ ID NO: 982, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 973; SEQ ID NO: 975; SEQ ID NO: 977; and SEQ ID NO: 979, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 961, or the variable heavy chain sequence of SEQ ID NO: 962, and/or one or more of the polynucleotide sequences of SEQ ID NO: 993; SEQ ID NO: 995; SEQ ID NO: 997; and SEQ ID NO: 999, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 981, or the variable light chain sequence of SEQ ID NO: 982, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or

alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 971 encoding the heavy chain sequence of SEQ ID NO: 961; the polynucleotide SEQ ID NO: 972 encoding the variable heavy chain sequence of SEQ ID NO: 962; the polynucleotide SEQ ID NO: 991 encoding the light chain sequence of SEQ ID NO: 981; the polynucleotide SEQ ID NO: 992 encoding the variable light chain sequence of SEQ ID NO: 982; polynucleotides encoding the CDRs (SEQ ID NO: 974; SEQ ID NO: 976; and SEQ ID NO: 978) of the heavy chain sequence of SEQ ID NO: 961, or the variable heavy chain sequence of SEQ ID NO: 962; polynucleotides encoding the CDRs (SEQ ID NO: 994; SEQ ID NO: 996; and SEQ ID NO: 998) of the light chain sequence of SEQ ID NO: 981, or the variable light chain sequence of SEQ ID NO: 982; polynucleotides encoding the FRs (SEQ ID NO: 973; SEQ ID NO: 975; SEQ ID NO: 977; and SEQ ID NO: 979) of the heavy chain sequence of SEQ ID NO: 961, or the variable heavy chain sequence of SEQ ID NO: 962; and polynucleotides encoding the FRs (SEQ ID NO: 993; SEQ ID NO: 995; SEQ ID NO: 997; and SEQ ID NO: 999) of the light chain sequence of SEQ ID NO: 981, or the variable light chain sequence of SEQ ID NO: 982.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H, the polynucleotides encoding the full length Ab10.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 971 encoding the heavy chain sequence of SEQ ID NO: 961, and the polynucleotide SEQ ID NO: 991 encoding the light chain sequence of SEQ ID NO: 981.

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab10.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab10.H or Fab fragments thereof, can be produced via expression of Ab10.H 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 Ab21**



In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 851 which encodes the heavy chain sequence of SEQ ID NO: 841 and which consists of the heavy chain variable  
5 region coding sequence of SEQ ID NO: 852 and the heavy chain constant region coding sequence of SEQ ID NO: 860.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain  
10 polypeptide sequence of SEQ ID NO: 842:  
cagtcgggtggaggagtcgggggctgcctggtcacgcctgggacacccctgacactcacctgcacagtcctctggaatcgacctcagtagctacta  
catgacctgggtccgccaggctccaggaaggggctggaatgggtcggttcattgatgctggtgtagcgcatatacgcgacctgggcaaaa  
ggccgattcaccatctcaaagcctgcaccaggtggatctgaaaatcaccagtcgcacaaccgaggacacggccacctattctgtgccagag  
atcttgactgtggggccgggcaccctggtcaccgtctcgagc (SEQ ID NO: 852).

15 In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 850:

gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcgccctgggctgcctggtaaggacta  
20 cttccccgaaccgtgtgaggtgtctgtggaactcaggcgccctgaccagcggtgcacaccttccggctgtcctacagtcctcaggactctactc  
cctcagcagcgtggtgacctgtccctccagcagcttgggcacccagacctaactctgcaacgtgaatcacaagcccagcaacaccaaggtgga  
caagaaagtgtgacccaaatctgtgacaaaactcacacatgccaccgtgccagcacctgaactcctggggggaccgtcagttctctcttc  
ccccaaaacccaaggacaccctcatgatctccggaccctgaggtcacatgctgtggtggacgtgagccacgaagaccctgaggtcaagtt  
caactggtacgtggacggcgtggaggtgcataatccaagacaaagccggggaggagcagtagccagcacgtaccgtgtggtcagcgtcct  
25 caccgtctcgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctc  
caaagccaaagggcagccccgagaaccacaggtgtacacctgtcccccatccgggaggagatgaccaagaaccaggtcagcctgacctgcc  
tggtcaaaggcttctatcccagcagatcgccgtggagtgaggagagcaatgggcagccggagagaacaactacaagaccacgcctcccgtgctgg  
actccgacggctccttctctctacagcaagctcacgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagagcctctcctgtctccgggtaaa (SEQ ID NO: 860).

30 In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 871 which encodes the light chain polypeptide sequence of SEQ ID NO: 861 and which consists of the light chain variable region coding sequence of SEQ ID NO: 872 and the light chain constant region coding sequence of SEQ ID NO: 880.

In another 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: 862:

5 gccgccgtgctgaccagactccatctcccggtgtctgcagctgtgggaggcacagtcagcatcagttgcaagtcagtgagagcggttatggatga  
ctacttagcctgggttcagcagaaaccaggggcagcctcccaagcaactgatctatgatgcacactctggcatctgggggtcccatcgcggttcaa  
aggcagtggtatctgggacacagttcactctcaccatcagcggcgtgcagtgtagcagtgctccacttactactgtgcaggcggttatgttagtgc  
agggtgtgcttccggcgaggaccgaggtgggtggtcaaact (SEQ ID NO: 872).

10 In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 870:

acggtagcggccccatctgtcttcatcttccgcatctgatgagcagttgaaatctggaactgcctctgttgctgtcctgtaataacttctatcc  
cagagaggccaaagtacagtgggaaggtggataacgccctccaatcgggtaactccaggagagtgtagcagagcaggacagcaaggacagc  
15 acctacagcctcagcagcacctgacgctgagcaagcagactacgagaacacaaagtctacgctgcgaagtcacccatcaggcgctgagc  
tcgccgctcacaagagcttcaacaggggagagtgt (SEQ ID NO: 880).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 854; SEQ ID NO: 856; and SEQ ID NO: 858, which correspond to polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 841, or the variable heavy chain sequence of SEQ ID NO: 842, and/or one or more of the polynucleotide sequences of SEQ ID NO: 874; SEQ ID NO: 876; and SEQ ID NO: 878, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 861, or the variable light chain sequence of SEQ ID NO: 862, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

30 In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 853; SEQ ID NO: 855; SEQ ID NO: 857; and SEQ ID NO: 859, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO:

- 841, or the variable heavy chain sequence of SEQ ID NO: 842, and/or one or more of the polynucleotide sequences of SEQ ID NO: 873; SEQ ID NO: 875; SEQ ID NO: 877; and SEQ ID NO: 879, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 861, or the variable light chain sequence of SEQ ID NO: 862, or combinations of these polynucleotide sequences.
- 5 In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.
- 10 The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 851 encoding the heavy chain
- 15 sequence of SEQ ID NO: 841; the polynucleotide SEQ ID NO: 852 encoding the variable heavy chain sequence of SEQ ID NO: 842; the polynucleotide SEQ ID NO: 871 encoding the light chain sequence of SEQ ID NO: 861; the polynucleotide SEQ ID NO: 872 encoding the variable light chain sequence of SEQ ID NO: 862; polynucleotides encoding the CDRs (SEQ ID NO: 854; SEQ ID NO: 856; and SEQ ID NO: 858) of the heavy chain sequence of SEQ ID NO: 841, or the variable heavy chain sequence of SEQ ID NO:
- 20 842; polynucleotides encoding the CDRs (SEQ ID NO: 874; SEQ ID NO: 876; and SEQ ID NO: 878) of the light chain sequence of SEQ ID NO: 861, or the variable light chain sequence of SEQ ID NO: 862; polynucleotides encoding the FRs (SEQ ID NO: 853; SEQ ID NO: 855; SEQ ID NO: 857; and SEQ ID NO: 859) of the heavy chain sequence of SEQ ID NO: 841, or the variable heavy chain sequence of SEQ ID NO: 842; and polynucleotides encoding the FRs (SEQ ID NO: 873; SEQ ID NO: 875; SEQ ID NO: 877; and
- 25 SEQ ID NO: 879) of the light chain sequence of SEQ ID NO: 861, or the variable light chain sequence of SEQ ID NO: 862.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect

30 to antibody Ab21, the polynucleotides encoding the full length Ab21 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 851 encoding the heavy chain sequence of SEQ ID NO: 841, and the polynucleotide SEQ ID NO: 871 encoding the light chain sequence of SEQ ID NO: 861.

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab21 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab21 or Fab fragments thereof, can be produced via expression of Ab21 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 Ab21.H

In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1211 which encodes the heavy chain sequence of SEQ ID NO: 1201 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1212 and the heavy chain constant region coding sequence of SEQ ID NO: 1220.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1202:

gaggtgcagcttggagctctggggaggcttggtccagcctgggggtccctgagactctctgtgcagcctctggaatcgacctcagtagcta  
ctacatgacctgggtccgtcaggctccagggaaggggctggagtggtcggattcattgatgtggtgtagcgatactacgcgacctgggca  
aaaggccgattcaccatctccagagacaattccaagaacaccgtgtatcttcaaatgaacagcctgagagctgaggacactgtgtgtttctg  
tgctagagatcttgacttggggccaaggacacctgtcaccgtctcgagc (SEQ ID NO: 1212).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1210:

gcctccaccaaggcccatcggtcttccccctggcaccctctccaagagcacctctgggggcacagcgccctgggctgcctggtcaaggacta  
ctccccgaaccggtagcgggtgtcgtggaactcaggcgccctgaccagcggtgcacacctcccggctgtcctacagtcctcaggactctactc  
ctcagcagcgtggtgacctgtccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga  
caagaaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgccagcactgaactcctggggggaccgtcagttctctcttc

ccccaaaaccaaggacacccctcatgatctccggaccctgaggtcacatgctggtggtggacgtgagccacgaagaccctgaggtcaagtt  
caactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgaggaggagcagtagccagcacgtaccgtggtgagcgtcct  
caccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagccccatcgagaaaaccatctc  
caaagccaaagggcagccccgagaaccacaggtgtacacccctgccccatccggaggagatgaccaagaaccaggtcagcctgacctgcc  
5 tggtaaaggcttctatcccagcgatcgcgtggagtgaggagcaatgggcagccggagaacaactacaagaccacgcctcccgctgctgg  
actccgagggctcttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 1220).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the  
10 polynucleotide sequence of SEQ ID NO: 1231 which encodes the light chain polypeptide sequence of  
SEQ ID NO: 1221 and which consists of the light chain variable region coding sequence of SEQ ID NO:  
1232 and the light chain constant region coding sequence of SEQ ID NO: 1240.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
15 consist of, the following polynucleotide sequence encoding the variable light chain polypeptide  
sequence of SEQ ID NO: 1222:

gagcccgctgacccagtcctctccaccctgtctgcatctgtaggagacagagtcaccatcacttgtaagtccagtgagagcgtttatggtgac  
tacttagcctggtttcagcagaaaccaggaaaagcccctaagcaactgatctatgatgcatccactctggcatctggagtcacatcaaggttcag  
cggcagtggtatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaactactactgtgcaggcggtatgttagtgc  
20 aggtgttgctttcgccggaggaaaccaaggtggaaatcaaacgt (SEQ ID NO: 1232).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
consist of, the following polynucleotide sequence encoding the constant light chain polypeptide  
sequence of SEQ ID NO: 1230:

25 acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtcctgctgaataacttctatcc  
cagagaggccaaagtacagtggagggtggataacgccctccaatcggttaactcccaggagagtgatcacagagcaggacagcaaggacagc  
acctacagcctcagcagccctgacgctgagcaaagcagactacgagaaacacaaagtctacgctgcgaagtcacccatcaggcctgagc  
tcgccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 1240).

30 In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 1214; SEQ ID NO: 1216; and SEQ ID NO: 1218, which correspond to  
polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO:  
1201, or the variable heavy chain sequence of SEQ ID NO: 1202, and/or one or more of the

polynucleotide sequences of SEQ ID NO: 1234; SEQ ID NO: 1236; and SEQ ID NO: 1238, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1221, or the variable light chain sequence of SEQ ID NO: 1222, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1213; SEQ ID NO: 1215; SEQ ID NO: 1217; and SEQ ID NO: 1219, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1201, or the variable heavy chain sequence of SEQ ID NO: 1202, and/or one or more of the polynucleotide sequences of SEQ ID NO: 1233; SEQ ID NO: 1235; SEQ ID NO: 1237; and SEQ ID NO: 1239, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1221, or the variable light chain sequence of SEQ ID NO: 1222, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1211 encoding the heavy chain sequence of SEQ ID NO: 1201; the polynucleotide SEQ ID NO: 1212 encoding the variable heavy chain sequence of SEQ ID NO: 1202; the polynucleotide SEQ ID NO: 1231 encoding the light chain sequence of SEQ ID NO: 1221; the polynucleotide SEQ ID NO: 1232 encoding the variable light chain sequence of SEQ ID NO: 1222; polynucleotides encoding the CDRs (SEQ ID NO: 1214; SEQ ID NO: 1216; and SEQ ID NO: 1218) of the heavy chain sequence of SEQ ID NO: 1201, or the variable heavy chain sequence of SEQ ID NO: 1202; polynucleotides encoding the CDRs (SEQ ID NO: 1234; SEQ ID NO: 1236; and SEQ ID NO: 1238) of the light chain sequence of SEQ ID NO: 1221, or the variable light chain sequence of SEQ ID NO: 1222; polynucleotides encoding the FRs (SEQ ID NO: 1213; SEQ ID NO: 1215; SEQ ID NO:

1217; and SEQ ID NO: 1219) of the heavy chain sequence of SEQ ID NO: 1201, or the variable heavy chain sequence of SEQ ID NO: 1202; and polynucleotides encoding the FRs (SEQ ID NO: 1233; SEQ ID NO: 1235; SEQ ID NO: 1237; and SEQ ID NO: 1239) of the light chain sequence of SEQ ID NO: 1221, or the variable light chain sequence of SEQ ID NO: 1222.

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In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H, the polynucleotides encoding the full length Ab21.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 1211 encoding the heavy chain sequence of SEQ ID NO: 1201, and the polynucleotide SEQ ID NO: 1231 encoding the light chain sequence of SEQ ID NO: 1221.

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Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab21.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab21.H or Fab fragments thereof, can be produced via expression of Ab21.H 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*.

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#### **Antibody Ab22**

In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 891 which encodes the heavy chain sequence of SEQ ID NO: 881 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 892 and the heavy chain constant region coding sequence of SEQ ID NO: 900.

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In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 882:

caggagcagctggaggagtcggggaggcctgggtccagcctgagggatccctgacactcacctgcacagcctctggattcgacttcagtagca  
atgcaatgtgctgggtccgcccagggtccagggaagggcctggagtggtcggtatccattataatgctgatggtaagaattattacgcgatttgg  
gcgaaaggccgattcaccatctccagaacctgctgaccacgggtgactctgcaaatgaccagtctgacagccgaggacacggccacctatttctg  
tgcgagagactttgacttggggccagggcacacctctcaccgtctcgagc (SEQ ID NO: 892).

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In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 890:

gcctccaccaaggcccatcggtcttcccctggcaccctcctcaagagcacctctgggggcacagcgccctgggtgctgcaaggacta  
10 cttccccgaacgggtgacgggtgctggaactcaggcgccctgaccagcggtgcacaccttccgggtgctctacagtcctcaggactctactc  
cctcagcagcgtggtgacctgcccctccagcagcttgggcacccagacatcatctgcaacgtgaatcacaagcccagcaaccaagggtgga  
cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgccagcacctgaactcctggggggaccgtcagttcttcttcc  
ccccaaaacccaaggacacctcatgatctccggacccctgaggtcacatgctggtgggtggacgtgagccagaagacctgagggtcaagtt  
caactggtacgtggagggcgtggaggtgcataatgccaagacaaagccggggaggagcagtagccagcacgtaccgtgtggtcagcgtctc  
15 caccgtcctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagccccatcgagaaaaccatctc  
caaagccaaagggcagccccgagaaccacaggtgtacacctgccccatcccgaggagatgaccaagaaccagggtcagctgacctgcc  
tggtcaaaggcttctatcccagcgacatgccgtggagtgaggagagcaatgggcagccggagaacaactacaagaccagcctcccgtgctgg  
actccgacggctccttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 900).

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In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 911 which encodes the light chain polypeptide sequence of SEQ ID NO: 901 and which consists of the light chain variable region coding sequence of SEQ ID NO: 912 and the light chain constant region coding sequence of SEQ ID NO: 920.

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In another 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: 902:

gcagccgtgctgaccagacaccatcgccgtgtctgcagctgtgggaggcacagtcacatcaattgccagtccagtcagagtggttatgataa  
30 cgactggttagcctggttcagcagaaaccagggcagcctccaagctcctgatctatctgacatccactctggcatctggagtcacatcgcggtt  
cagcggcagtggtatctgggacacagttcactctcaccatcagtggtgtgacgtgtgacgtgctgccacttactactgtctaggcggtatgatga  
agatggtgatacgcatgttttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 912).



In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 910:

acggtagcggcccatctgtcttcatcttccgccatctgatgagcagttgaaatctggaactgcctctgttgctgctgaataacttctatcc  
5 cagagaggccaaagtacagtggagggtgataacgccctccaatcgggtaactcccaggagagtgacagagcaggacagcaaggacagc  
acctacagcctcagcagcaccctgacgtgagcaaagcagactacgagaaacaaaagtctacgcctgcgaagtcacccatcagggcctgagc  
tcgccgctcacaagagcttcaacaggggagagtggt (SEQ ID NO: 920).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
10 binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 894; SEQ ID NO: 896; and SEQ ID NO: 898, which correspond to  
polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO:  
881, or the variable heavy chain sequence of SEQ ID NO: 882, and/or one or more of the  
polynucleotide sequences of SEQ ID NO: 914; SEQ ID NO: 916; and SEQ ID NO: 918, which correspond  
15 to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 901, or the variable light  
chain sequence of SEQ ID NO: 902, or combinations of these polynucleotide sequences. In another  
embodiment of the invention, the polynucleotides encoding the antibodies of the invention or  
antigen-binding fragments thereof comprise, or alternatively consist of, combinations of  
polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain  
20 sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 893; SEQ ID NO: 895; SEQ ID NO: 897; and SEQ ID NO: 899, which correspond  
25 to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO:  
881, or the variable heavy chain sequence of SEQ ID NO: 882, and/or one or more of the  
polynucleotide sequences of SEQ ID NO: 913; SEQ ID NO: 915; SEQ ID NO: 917; and SEQ ID NO: 919,  
which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 901, or the  
variable light chain sequence of SEQ ID NO: 902, or combinations of these polynucleotide sequences.  
30 In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention  
or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs,  
the variable heavy chain and variable light chain sequences, and the heavy chain and light chain  
sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides

5 encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 891 encoding the heavy chain sequence of SEQ ID NO: 881; the polynucleotide SEQ ID NO: 892 encoding the variable heavy chain sequence of SEQ ID NO: 882; the polynucleotide SEQ ID NO: 911 encoding the light chain sequence of SEQ ID NO: 901; the polynucleotide SEQ ID NO: 912 encoding the variable light chain sequence of SEQ ID NO: 902; polynucleotides encoding the CDRs (SEQ ID NO: 894; SEQ ID NO: 896; and SEQ ID NO: 898)

10 of the heavy chain sequence of SEQ ID NO: 881, or the variable heavy chain sequence of SEQ ID NO: 882; polynucleotides encoding the CDRs (SEQ ID NO: 914; SEQ ID NO: 916; and SEQ ID NO: 918) of the light chain sequence of SEQ ID NO: 901, or the variable light chain sequence of SEQ ID NO: 902; polynucleotides encoding the FRs (SEQ ID NO: 893; SEQ ID NO: 895; SEQ ID NO: 897; and SEQ ID NO: 899) of the heavy chain sequence of SEQ ID NO: 881, or the variable heavy chain sequence of SEQ ID

15 NO: 882; and polynucleotides encoding the FRs (SEQ ID NO: 913; SEQ ID NO: 915; SEQ ID NO: 917; and SEQ ID NO: 919) of the light chain sequence of SEQ ID NO: 901, or the variable light chain sequence of SEQ ID NO: 902.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively

20 consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab22, the polynucleotides encoding the full length Ab22 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 891 encoding the heavy chain sequence of SEQ ID NO: 881, and the polynucleotide SEQ ID NO: 911 encoding the light chain sequence of SEQ ID NO: 901.

25

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by

30 enzymatic digestion (e.g., papain) of Ab22 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab22 or Fab fragments thereof, can be produced via expression of Ab22 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 Ab23

- 5 In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 931 which encodes the heavy chain sequence of SEQ ID NO: 921 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 932 and the heavy chain constant region coding sequence of
- 10 SEQ ID NO: 940.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 922:

- 15 cagtcggtggaggagtcggtgggtgcctgtcacgcctgggacacccctgacactcacctgcacgtctctggattctccctcaataactatgc  
aatgagctgggtccgccaggctccagggaagggtggaatggatcggaatcatgggtgtaatatcatatcacatactacgcgagctggggcaa  
aggcggattcaccatctcaaaacctgcaccaggtggtatctgaaaatgaccagtctgacaaccgaggacacggccacctattctgtactaga  
gagatccgtgatgatggtgatagttctgataagttgtggggcccgggcacccctgtcaccgtctcgagc (SEQ ID NO: 932).

- 20 In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 930:

- gcctccaccaagggcccatcggtcttccccctggcacccctctccaagagcacctctgggggcacagcgccctgggctgcctggtcaaggacta  
cttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggtgcacaccttccggctgtcctacagtctcaggactctactc  
25 cctcagcagcgtggtgacctgacctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaagggtgga  
cgcgagagttgagcccaaatctgtgacaaaactcacatgcccaccgtgccagcacctgaactcctggggggaccgtcagttctctcttcc  
ccccaaaaccaaggacacctcatgatctccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagacctgaggtcaagtt  
caactggtacgtggacggcgtggaggtgcataatgccaagacaaagccggggaggagcagtagccagcacgtaccgtgtggtcagcgtcct  
caccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagccccatcgagaaaaccatctc  
30 caaagccaaaggcgagccccgagaaccacaggtgtacacctgccccatcccgaggagatgaccaagaaccaggtcagcctgacctgcc  
tggtcaaaggcttctatccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgctgctgg  
actccgacggctcttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgatgag  
gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 940).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 951 which encodes the light chain polypeptide sequence of SEQ ID NO: 941 and which consists of the light chain variable region coding sequence of SEQ ID NO: 952 and the light chain constant region coding sequence of SEQ ID NO: 960.

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In another 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: 942:

gccatcaaaatgaccagactccatcctccgtgtctgcagctgtgggaggcacagtcaccatcaattgccaggccagtgaggacatttacacca  
10 atttagcctggtatcagcagaaaccagggcagcctcccaacctctgatctatgatgcacatccgatctggggtcccgctgcggttcagcg  
gcagtgaggatgggacacagttcactctcaccatcagcgcgtgcagtgtaagatgctgccacttactgtcaagggttgcttgaggtagt  
aatactgggttatggtccgcttcggcggagggaccgaggtgggtggtcaaacgt (SEQ ID NO: 952).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
15 consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 950:

acggtagcgggcccatctgtcttcatcttccgccatctgatgagcagtgaaatctggaactgcctctgtgtgctgctgaataacttctatcc  
cagagaggccaaagtacagtgggaaggtggataacgccctccaatcgggtaactccaggagagtgacagagcaggacagcaaggacagc  
acctacagcctcagcagcacctgacgctgagcaagcagactacgagaaacacaaagtctacgcctgcaagtcacccatcagggcctgagc  
20 tcgcccgtcacaagagcttcaacaggggagagtggt (SEQ ID NO: 960).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 934; SEQ ID NO: 936; and SEQ ID NO: 938, which correspond to  
25 polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 921, or the variable heavy chain sequence of SEQ ID NO: 922, and/or one or more of the polynucleotide sequences of SEQ ID NO: 954; SEQ ID NO: 956; and SEQ ID NO: 958, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 941, or the variable light chain sequence of SEQ ID NO: 942, or combinations of these polynucleotide sequences. In another  
30 embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 933; SEQ ID NO: 935; SEQ ID NO: 937; and SEQ ID NO: 939, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 921, or the variable heavy chain sequence of SEQ ID NO: 922, and/or one or more of the polynucleotide sequences of SEQ ID NO: 953; SEQ ID NO: 955; SEQ ID NO: 957; and SEQ ID NO: 959, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 941, or the variable light chain sequence of SEQ ID NO: 942, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 931 encoding the heavy chain sequence of SEQ ID NO: 921; the polynucleotide SEQ ID NO: 932 encoding the variable heavy chain sequence of SEQ ID NO: 922; the polynucleotide SEQ ID NO: 951 encoding the light chain sequence of SEQ ID NO: 941; the polynucleotide SEQ ID NO: 952 encoding the variable light chain sequence of SEQ ID NO: 942; polynucleotides encoding the CDRs (SEQ ID NO: 934; SEQ ID NO: 936; and SEQ ID NO: 938) of the heavy chain sequence of SEQ ID NO: 921, or the variable heavy chain sequence of SEQ ID NO: 922; polynucleotides encoding the CDRs (SEQ ID NO: 954; SEQ ID NO: 956; and SEQ ID NO: 958) of the light chain sequence of SEQ ID NO: 941, or the variable light chain sequence of SEQ ID NO: 942; polynucleotides encoding the FRs (SEQ ID NO: 933; SEQ ID NO: 935; SEQ ID NO: 937; and SEQ ID NO: 939) of the heavy chain sequence of SEQ ID NO: 921, or the variable heavy chain sequence of SEQ ID NO: 922; and polynucleotides encoding the FRs (SEQ ID NO: 953; SEQ ID NO: 955; SEQ ID NO: 957; and SEQ ID NO: 959) of the light chain sequence of SEQ ID NO: 941, or the variable light chain sequence of SEQ ID NO: 942.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab23, the polynucleotides encoding the full length Ab23 antibody comprise, or

alternatively consist of, the polynucleotide SEQ ID NO: 931 encoding the heavy chain sequence of SEQ ID NO: 921, and the polynucleotide SEQ ID NO: 951 encoding the light chain sequence of SEQ ID NO: 941.

- 5 Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab23 following expression of the full-length polynucleotides in a
- 10 suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab23 or Fab fragments thereof, can be produced via expression of Ab23 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*.

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#### Antibody Ab10.H2

- In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1291 which
- 20 encodes the heavy chain sequence of SEQ ID NO: 1281 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1292 and the heavy chain constant region coding sequence of SEQ ID NO: 1300.

- In another embodiment of the invention, the polynucleotides of the invention comprise, or
- 25 alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1282:

gagggtgcagcttgaggagctggggaggcctgtccagcctgggggtccctgagactctcctgtgcagcctctggaatcgacctcaatagcta  
ctacatgacctgggtccgtcaggctccaggaaggggctggagtgatcggttcattgatgctgggtgacgcatactacgcgagctgggcg  
aaaggccgattcaccatctccagagacaattccaagaacaccgtgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattctg  
30 tgctagagatcttgacttggggccaaggaccctcgtcaccgtctcgagc (SEQ ID NO: 1292).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1290:

gcctccaccaagggcccatcgggtcttccccctggcaccctctccaagagcacctctgggggcacagcgccctgggctgcttggtcaaggacta  
cttccccgaaccggtgacgggtgctggaactcaggcgccctgaccagcggtgcacaccttcccggtgtctactcctcaggactctactc  
cctcagcagcgtggtgacctgcccctcagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga  
caagaaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgccagcacctgaactcctggggggaccgtcagtcttctcttcc  
5 ccccaaaacccaaggacacctcatgatctcccgaccctgaggtcacatgctggtggtggacgtgagccacgaagacctgaggtaagtt  
caactgggtacgtggacggcgtggaggtgcataatgccaagacaaagccgaggaggagcagtagccagcacgtaccgtgtggtcagcgtcct  
caccgtcctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccatcgagaaaacctctc  
caagccaaagggcagccccgagaaccacaggtgtacacctgccccatcccggaggagatgaccaagaaccaggtcagcctgacctgcc  
tggtcaaaggcttctatcccagcagcatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgctcccgtgctgg  
10 actccgacggctccttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctctatgctccgtatgcatgag  
gctctgcacaaccactacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 1300).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the  
polynucleotide sequence of SEQ ID NO: 1311 which encodes the light chain polypeptide sequence of  
15 SEQ ID NO: 1301 and which consists of the light chain variable region coding sequence of SEQ ID NO:  
1312 and the light chain constant region coding sequence of SEQ ID NO: 1320.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
consist of, the following polynucleotide sequence encoding the variable light chain polypeptide  
20 sequence of SEQ ID NO: 1302:

gccgtgctgaccagtcctctccacctgtctgcatctgtaggagacagtcacatcacttgtcagtcagtgagagtggttacggtaactact  
tagcctgggtttcagcagaaaccaggaaaagccctaagttcctgatctatgaagcatcacaactggaatctggagtcctcaaggttcagcgg  
cagtggtatctggaacagaattcactctcaccatcagcagcctgcagcctgatgttttcaactactactgtgcaggcggatattagtgaaag  
tgttgctttcggcggaggaaccaaggtggaaatcaaact (SEQ ID NO: 1312).

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In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
consist of, the following polynucleotide sequence encoding the constant light chain polypeptide  
sequence of SEQ ID NO: 1310:

acggtagcggcccatctgtcttcatcttccgccatctgatgagcagtgaaatctggaactgcctctgtgtgctgctgaataacttctatcc  
30 cagagaggccaaagtacagtggagggtggataacgccctccaatcgggtaactcccaggagagtgatcacagagcaggacagcaaggacagc  
acctacagcctcagcagcaccctgacgtgagcaagcagactacgagaaacacaaagtctacgcctgcaagtcacccatcagggcctgagc  
tcgccgtcacaaagagcttcaacaggggagagtggt (SEQ ID NO: 1320).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1294; SEQ ID NO: 1296; and SEQ ID NO: 1298, which correspond to polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1281, or the variable heavy chain sequence of SEQ ID NO: 1282, and/or one or more of the polynucleotide sequences of SEQ ID NO: 1314; SEQ ID NO: 1316; and SEQ ID NO: 1318, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1301, or the variable light chain sequence of SEQ ID NO: 1302, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1293; SEQ ID NO: 1295; SEQ ID NO: 1297; and SEQ ID NO: 1299, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1281, or the variable heavy chain sequence of SEQ ID NO: 1282, and/or one or more of the polynucleotide sequences of SEQ ID NO: 1313; SEQ ID NO: 1315; SEQ ID NO: 1317; and SEQ ID NO: 1319, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1301, or the variable light chain sequence of SEQ ID NO: 1302, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1291 encoding the heavy chain sequence of SEQ ID NO: 1281; the polynucleotide SEQ ID NO: 1292 encoding the variable heavy chain sequence of SEQ ID NO: 1282; the polynucleotide SEQ ID NO: 1311 encoding the light chain sequence of SEQ ID NO: 1301; the polynucleotide SEQ ID NO: 1312 encoding the variable light chain sequence



of SEQ ID NO: 1302; polynucleotides encoding the CDRs (SEQ ID NO: 1294; SEQ ID NO: 1296; and SEQ ID NO: 1298) of the heavy chain sequence of SEQ ID NO: 1281, or the variable heavy chain sequence of SEQ ID NO: 1282; polynucleotides encoding the CDRs (SEQ ID NO: 1314; SEQ ID NO: 1316; and SEQ ID NO: 1318) of the light chain sequence of SEQ ID NO: 1301, or the variable light chain sequence of  
5 SEQ ID NO: 1302; polynucleotides encoding the FRs (SEQ ID NO: 1293; SEQ ID NO: 1295; SEQ ID NO: 1297; and SEQ ID NO: 1299) of the heavy chain sequence of SEQ ID NO: 1281, or the variable heavy chain sequence of SEQ ID NO: 1282; and polynucleotides encoding the FRs (SEQ ID NO: 1313; SEQ ID NO: 1315; SEQ ID NO: 1317; and SEQ ID NO: 1319) of the light chain sequence of SEQ ID NO: 1301, or the variable light chain sequence of SEQ ID NO: 1302.

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In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H2, the polynucleotides encoding the full length Ab10.H2 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 1291 encoding the heavy chain sequence of  
15 SEQ ID NO: 1281, and the polynucleotide SEQ ID NO: 1311 encoding the light chain sequence of SEQ ID NO: 1301.

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, or in fungal,  
20 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab10.H2 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab10.H2 or Fab fragments thereof, can be produced via expression of Ab10.H2 polynucleotides in mammalian  
25 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.H3**

30 In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1331 which encodes the heavy chain sequence of SEQ ID NO: 1321 or 1604 and which consists of the heavy chain

variable region coding sequence of SEQ ID NO: 1332 and the heavy chain constant region coding sequence of SEQ ID NO: 1340.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1322:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggaatcgacctcaatagcta  
ctacatgacctgggtccgtcaggctccagggaaggggctggagtggatcggtcattgatgctgggtgacgcatactacgcgagctgggcg  
aaaggccgattcacatctccagagacaattccaagaacaccgtgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattctg  
tgctagagatcttactgtggggccaaggacacctgtcaccgtctcgagc (SEQ ID NO: 1332).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1330:

gcctccaccaagggcccatcggtcttcccctggcaccctctccaagagcacctctgggggcacagcggcctgggctgcctggcaaggacta  
cttccccgaacgggtgacgggtgctgtggaactcaggcgccctgaccagcggcgtgcacaccttccggctgtcctacagtctcaggactctactc  
cctcagcagcgtggtgacctgacctccagcagcttgggcacccagacctacatctgcaactggaatcacaagcccagcaacaccaaggtgga  
caagaaagttgagcccaaatcttgtagaaaaactcacatgcccaccgtgccagcacctgaactcctggggggaccgtcagttctctcttcc  
ccccaaaacccaaggacacctcatgatctccggacccctgaggtcacatgctgtggtggagctgagccacgaagacctgaggtcaagtt  
caactggtagctggacggcgtggaggtgcataatccaagacaaagccgggaggagcagtagccagcacgtaccgtgtgtgtagcgtctc  
caccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccatcgagaaaacctctc  
caaagccaaagggcagccccgagaaccacaggtgtacacctgcccccatcccgaggagatgaccaagaaccaggtcagcctgacctgcc  
tggtcaaaggcttctatcccagcgacatcgctggagtgggagagcaatgggcagccggagaacaactacaagaccacgctccgtgctgg  
actccgacggctcttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagacacctctcctgtctccggtaaa (SEQ ID NO: 1340).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1351 which encodes the light chain polypeptide sequence of SEQ ID NO: 1341 and which consists of the light chain variable region coding sequence of SEQ ID NO: 1352 and the light chain constant region coding sequence of SEQ ID NO: 1360.

In another 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: 1342:

gacatccagctgacccagctctctccacctgtctgcatctgtaggagacagagtcacatcacttgctcagtcagtgagagtggttacggtaac  
tacttagcctgggttcagcagaaaccaggaagcccttaagttcctgatctatgaagcatccaaactggaatctggagtgccatcaagggttcag  
cggcagtggtatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtgcaggcggtgatattagtga  
agggtgtgctttcggcggaggaaccaagggtggaaatcaaacgt (SEQ ID NO: 1352).

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In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 1350:

acggtagcggcccatctgtcttcatcttccgccatctgatgagcagtgaaatctggaactgcctctgttggtgctgctgaataacttctatcc  
10 cagagaggccaaagtacagtggagggtggataacgccctcaatcgggtaactcccaggagagtggtcacagagcaggacagcaaggacagc  
acctacagcctcagcagcacctgacgctgagcaagcagactacgagaaacacaaagtctacgcctgcgaagtacccatcagggcctgagc  
tcgccgtcacaaagagcttcaacaggggagagtggt (SEQ ID NO: 1360).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
15 binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 1334; SEQ ID NO: 1336; and SEQ ID NO: 1338, which correspond to  
polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO:  
1321 or 1604, or the variable heavy chain sequence of SEQ ID NO: 1322, and/or one or more of the  
polynucleotide sequences of SEQ ID NO: 1354; SEQ ID NO: 1356; and SEQ ID NO: 1358, which  
20 correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1341, or the  
variable light chain sequence of SEQ ID NO: 1342, or combinations of these polynucleotide sequences.  
In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention  
or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of  
polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain  
25 sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 1333; SEQ ID NO: 1335; SEQ ID NO: 1337; and SEQ ID NO: 1339, which  
30 correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of  
SEQ ID NO: 1321 or 1604, or the variable heavy chain sequence of SEQ ID NO: 1322, and/or one or  
more of the polynucleotide sequences of SEQ ID NO: 1353; SEQ ID NO: 1355; SEQ ID NO: 1357; and  
SEQ ID NO: 1359, which correspond to the FRs (constant regions) of the light chain sequence of SEQ  
ID NO: 1341, or the variable light chain sequence of SEQ ID NO: 1342, or combinations of these

polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

5

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1331 encoding the heavy chain sequence of SEQ ID NO: 1321 or 1604; the polynucleotide SEQ ID NO: 1332 encoding the variable heavy chain sequence of SEQ ID NO: 1322; the polynucleotide SEQ ID NO: 1351 encoding the light chain sequence of SEQ ID NO: 1341; the polynucleotide SEQ ID NO: 1352 encoding the variable light chain sequence of SEQ ID NO: 1342; polynucleotides encoding the CDRs (SEQ ID NO: 1334; SEQ ID NO: 1336; and SEQ ID NO: 1338) of the heavy chain sequence of SEQ ID NO: 1321 or 1604, or the variable heavy chain sequence of SEQ ID NO: 1322; polynucleotides encoding the CDRs (SEQ ID NO: 1354; SEQ ID NO: 1356; and SEQ ID NO: 1358) of the light chain sequence of SEQ ID NO: 1341, or the variable light chain sequence of SEQ ID NO: 1342; polynucleotides encoding the FRs (SEQ ID NO: 1333; SEQ ID NO: 1335; SEQ ID NO: 1337; and SEQ ID NO: 1339) of the heavy chain sequence of SEQ ID NO: 1321 or 1604, or the variable heavy chain sequence of SEQ ID NO: 1322; and polynucleotides encoding the FRs (SEQ ID NO: 1353; SEQ ID NO: 1355; SEQ ID NO: 1357; and SEQ ID NO: 1359) of the light chain sequence of SEQ ID NO: 1341, or the variable light chain sequence of SEQ ID NO: 1342.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H3, the polynucleotides encoding the full length Ab10.H3 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 1331 encoding the heavy chain sequence of SEQ ID NO: 1321 or 1604, and the polynucleotide SEQ ID NO: 1351 encoding the light chain sequence of SEQ ID NO: 1341.

30

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by

enzymatic digestion (e.g., papain) of Ab10.H3 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab10.H3 or Fab fragments thereof, can be produced via expression of Ab10.H3 polynucleotides in mammalian cells such as CHO, NSO, or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for  
5 example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

#### Antibody Ab10.H4

In one embodiment, the invention is further directed to polynucleotides encoding antibody  
10 polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1371 which encodes the heavy chain sequence of SEQ ID NO: 1361 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1372 and the heavy chain constant region coding sequence of  
15 SEQ ID NO: 1380.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1362:

gagggtgcagcttgaggagctgggggaggcttggtccagcctggggggtccctgagactctcctgtgcagcctctggaatcgacctcaatagcta  
20 ctacatgacctgggtccgtcagggtccagggaaggggctggagtggtcggttcattgatctggtggtgacgcatactacgcgagctgggcg  
aaagccgattcaccatctccagagacaattccaagaacaccgtgtatcttcaaataaacagcctgagagctgaggacactgctgtgtattctg  
tgctagagatcttgactgtggggccaaggacccctcgctaccgtctcgagc (SEQ ID NO: 1372).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
25 consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1370:

gcctccaccaagggcccatcggtcttccccctggcaccctctccaagagcacctctgggggcacagcgccctgggctgcctggtcaaggacta  
cttccccgaaccgggtgacgggtgctggaactcaggcgccctgaccagcggtgcacaccttccggctgtcctacagctcctcaggactctactc  
cctcagcagcgtggtgacctgcccctccagcagcttgggcaccagacctacatctgcaacgtgaatcacaagcccagcaaccaaggtgga  
30 caagaaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgccagcacctgaactcctggggggaccgtcagttctctcttcc  
ccccaaacccaaggacacctcatgatctccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagacctgaggtcaagtt  
caactggtacgtggacggcgtggaggtgcataatgccaagacaaagcgcgaggagcagtagccagcacgtaccgtgtggtcagcgtcct  
caccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagccccatcgagaaaaccatctc  
caaagccaaagggcagccccgagaaccacaggtgtacacctgccccatcccggaggagatgaccaagaaccaggtcagcctgacctgcc

tgggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctccgtgctgg  
actccgacggctccttctctctacagcaagctcacctggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 1380).

- 5 In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1391 which encodes the light chain polypeptide sequence of SEQ ID NO: 1381 and which consists of the light chain variable region coding sequence of SEQ ID NO: 1392 and the light chain constant region coding sequence of SEQ ID NO: 1400.

- 10 In another 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: 1382:

gacatcgtgctgacctcgtctctccacctgtctgcatctgtaggagacagagtcacatcacttgctcagtcagtgagtggttacggtaact  
acttagcctgggttcagcagaaaccagaaaagccctaagttcctgatctatgaagcatcctaaactggaatctggagtcctcaaggttcagc  
15 ggcagtggtatctggaacagaattcactctcaccatcagcagcctgagcctgatgattttgcaacttactactgtgcaggcgggtgatattagtga  
gggtgtgctttcggcggagggaaccaaggtggaatcaaact (SEQ ID NO: 1392).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide  
20 sequence of SEQ ID NO: 1390:

acggtagcggcccatctgtcttcatcttccgccatctgatgagcagttgaaatctggaactgcctctgttgctgctgtaataacttctatcc  
cagagaggccaaagtacagtggagggtgataacgcctccaatcgggtaactcccaggagagtgacacagagcaggacagcaaggacagc  
acctacagcctcagcagccctgacgtgagcaagcagactacgagaacacaaagtctacgcctgcgaagtcacccatcaggcctgagc  
tcgccgtcacaagagcttcaacaggggagagtg (SEQ ID NO: 1400).

- 25 In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1374; SEQ ID NO: 1376; and SEQ ID NO: 1378, which correspond to polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1361, or the variable heavy chain sequence of SEQ ID NO: 1362, and/or one or more of the  
30 polynucleotide sequences of SEQ ID NO: 1394; SEQ ID NO: 1396; and SEQ ID NO: 1398, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1381, or the variable light chain sequence of SEQ ID NO: 1382, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention

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

- 5 In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1373; SEQ ID NO: 1375; SEQ ID NO: 1377; and SEQ ID NO: 1379, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1361, or the variable heavy chain sequence of SEQ ID NO: 1362, and/or one or more of the
- 10 polynucleotide sequences of SEQ ID NO: 1393; SEQ ID NO: 1395; SEQ ID NO: 1397; and SEQ ID NO: 1399, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1381, or the variable light chain sequence of SEQ ID NO: 1382, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more
- 15 of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

- The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment,
- 20 polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1371 encoding the heavy chain sequence of SEQ ID NO: 1361; the polynucleotide SEQ ID NO: 1372 encoding the variable heavy chain sequence of SEQ ID NO: 1362; the polynucleotide SEQ ID NO: 1391 encoding the light chain sequence
- 25 of SEQ ID NO: 1381; the polynucleotide SEQ ID NO: 1392 encoding the variable light chain sequence of SEQ ID NO: 1382; polynucleotides encoding the CDRs (SEQ ID NO: 1374; SEQ ID NO: 1376; and SEQ ID NO: 1378) of the heavy chain sequence of SEQ ID NO: 1361, or the variable heavy chain sequence of SEQ ID NO: 1362; polynucleotides encoding the CDRs (SEQ ID NO: 1394; SEQ ID NO: 1396; and SEQ ID NO: 1398) of the light chain sequence of SEQ ID NO: 1381, or the variable light chain sequence of
- 30 SEQ ID NO: 1382; polynucleotides encoding the FRs (SEQ ID NO: 1373; SEQ ID NO: 1375; SEQ ID NO: 1377; and SEQ ID NO: 1379) of the heavy chain sequence of SEQ ID NO: 1361, or the variable heavy chain sequence of SEQ ID NO: 1362; and polynucleotides encoding the FRs (SEQ ID NO: 1393; SEQ ID NO: 1395; SEQ ID NO: 1397; and SEQ ID NO: 1399) of the light chain sequence of SEQ ID NO: 1381, or the variable light chain sequence of SEQ ID NO: 1382.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H4, the polynucleotides encoding the full length Ab10.H4 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 1371 encoding the heavy chain sequence of SEQ ID NO: 1361, and the polynucleotide SEQ ID NO: 1391 encoding the light chain sequence of SEQ ID NO: 1381.

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab10.H4 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab10.H4 or Fab fragments thereof, can be produced via expression of Ab10.H4 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*.

#### 20 Antibody Ab10.H5

In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1411 which encodes the heavy chain sequence of SEQ ID NO: 1401 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1412 and the heavy chain constant region coding sequence of SEQ ID NO: 1420.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1402:

gagggtgcagcttgaggagctgggggaggccttggtccagcctggggggtccctgagactctcctgtgcagcctctggaatcgacctcaatagcta  
ctacatgacctgggtccgtcaggctccagggaaggggctggagtggtatcggtgacgcatactacgcgagctgggctg  
aaagccgattcaccatctccagagacaattccaagaacaccgtgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtatttctg  
tgctagagatcttgactgtggggccaaggaccctgtcaccgtctcgagc (SEQ ID NO: 1412).



In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1410:

5 gcctccaccaaggcccatcggtcttcccctggcaccctcctcaagagcacctctgggggcacagcgccctgggctgcctggtcaaggacta  
cttccccgaaccgggtgacgggtgctggaactcaggcgccctgaccagcggtgcacaccttccggctgtcctacagtcctcaggactctactc  
cctcagcagcgtggtgacctgcccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaaccaaggtgga  
caagaaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgccagcacctgaactcctggggggaccgtcagtccttctctcc  
cccaaaacccaaggacaccctcatgatctccggacccctgaggtcacatgctggtggtggacgtgagccacgaagaccctgaggtcaagtt  
10 caactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgaggaggagcagtagccagcacgtaccgtgtggtcagcgtcct  
caccgtctcgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagcccccatcgagaaaaccatctc  
caaagccaaagggcagccccgagaaccaaggtgtacacccctgccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcc  
tggtcaaaggcttctatcccagcgacatcgctggagtgaggagcaatgggcagccggagaacaactacaagaccacgctccctgctggtg  
actccgacggctcttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
15 gctctgcacaaccactacacgcagaagagcctctcctgtctccgggtaaa (SEQ ID NO: 1420).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1431 which encodes the light chain polypeptide sequence of SEQ ID NO: 1421 and which consists of the light chain variable region coding sequence of SEQ ID NO: 1432 and the light chain constant region coding sequence of SEQ ID NO: 1440.

In another 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: 1422:

25 cagctgaccagtcctcttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcagtcagtgagagtggttacggtaactacttag  
cctggtttcagcagaaaaccaggaagccctaagttctgatctatgaagcatccaaactggaatctggagtcctcaaggttcagcggcag  
tggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtgcaggcgggtgatattaggaaggtg  
tgctttcggcggaggaaccaaggtggaaatcaaact (SEQ ID NO: 1432).

30 In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 1430:

acggtagcggccccatctgtctcatcttccgcatctgatgagcagtgaaatctggaactgcctctgtgtgctgctgaataacttctatcc  
cagagaggccaaagtacagtggagggtggataacgcctccaatcgggtaactccaggagagtgacagagcaggacagcaaggacagc

acctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagc  
tcgccgctcacaagagcttcaacaggggagagtgt (SEQ ID NO: 1440).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
5 binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 1414; SEQ ID NO: 1416; and SEQ ID NO: 1418, which correspond to  
polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO:  
1401, or the variable heavy chain sequence of SEQ ID NO: 1402, and/or one or more of the  
polynucleotide sequences of SEQ ID NO: 1434; SEQ ID NO: 1436; and SEQ ID NO: 1438, which  
10 correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1421, or the  
variable light chain sequence of SEQ ID NO: 1422, or combinations of these polynucleotide sequences.  
In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention  
or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of  
polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain  
15 sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 1413; SEQ ID NO: 1415; SEQ ID NO: 1417; and SEQ ID NO: 1419, which  
20 correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of  
SEQ ID NO: 1401, or the variable heavy chain sequence of SEQ ID NO: 1402, and/or one or more of the  
polynucleotide sequences of SEQ ID NO: 1433; SEQ ID NO: 1435; SEQ ID NO: 1437; and SEQ ID NO:  
1439, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1421,  
or the variable light chain sequence of SEQ ID NO: 1422, or combinations of these polynucleotide  
25 sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of  
the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more  
of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light  
chain sequences set forth above, including all of them.

30 The invention also contemplates polynucleotide sequences including one or more of the  
polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment,  
polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or  
alternatively consist of, one, two, three or more, including all of the following polynucleotides  
encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1411 encoding the heavy chain

sequence of SEQ ID NO: 1401; the polynucleotide SEQ ID NO: 1412 encoding the variable heavy chain sequence of SEQ ID NO: 1402; the polynucleotide SEQ ID NO: 1431 encoding the light chain sequence of SEQ ID NO: 1421; the polynucleotide SEQ ID NO: 1432 encoding the variable light chain sequence of SEQ ID NO: 1422; polynucleotides encoding the CDRs (SEQ ID NO: 1414; SEQ ID NO: 1416; and SEQ ID NO: 1418) of the heavy chain sequence of SEQ ID NO: 1401, or the variable heavy chain sequence of SEQ ID NO: 1402; polynucleotides encoding the CDRs (SEQ ID NO: 1434; SEQ ID NO: 1436; and SEQ ID NO: 1438) of the light chain sequence of SEQ ID NO: 1421, or the variable light chain sequence of SEQ ID NO: 1422; polynucleotides encoding the FRs (SEQ ID NO: 1413; SEQ ID NO: 1415; SEQ ID NO: 1417; and SEQ ID NO: 1419) of the heavy chain sequence of SEQ ID NO: 1401, or the variable heavy chain sequence of SEQ ID NO: 1402; and polynucleotides encoding the FRs (SEQ ID NO: 1433; SEQ ID NO: 1435; SEQ ID NO: 1437; and SEQ ID NO: 1439) of the light chain sequence of SEQ ID NO: 1421, or the variable light chain sequence of SEQ ID NO: 1422.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H5, the polynucleotides encoding the full length Ab10.H5 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 1411 encoding the heavy chain sequence of SEQ ID NO: 1401, and the polynucleotide SEQ ID NO: 1431 encoding the light chain sequence of SEQ ID NO: 1421.

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab10.H5 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab10.H5 or Fab fragments thereof, can be produced via expression of Ab10.H5 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.H6**

In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the

invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1451 which encodes the heavy chain sequence of SEQ ID NO: 1441 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1452 and the heavy chain constant region coding sequence of SEQ ID NO: 1460.

5

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1442:

gaggtgcagcttgaggagctgggggaggcttggtccagcctggggggtccctgagactctcctgtgcagcctctggaatcgacctcaatagcta  
10 ctacatgacctgggtccgtcaggctccagggaagggtctggagtgatcggattcattgatctggtggtgacgcatactacgcagctgggagc  
aaaggccgattcaccatctcagagacaattcaagaacaccgtgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattctg  
tgctagagatcttgactgtggggccaaggacacctcgaccgtctcgagc (SEQ ID NO: 1452).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
15 consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1450:

gcctccaccaaggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggacta  
cttccccgaaccggtgacgggtgctggtgaactcaggcgccctgaccagcggcgtgcacaccttccggctgtcctacagtctcaggactctactc  
cctcagcagcgtggtgacctgacctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaagggtgga  
20 caagaaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgccagcacctgaactcctggggggaccgtcagttcttcttcc  
ccccaaaaccaaggacacctcatgatctccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagtt  
caactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgaggaggagcagtagccagcacgtaccgtgtggtcagcgtcct  
caccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagcccccatcgagaaaaccatctc  
caaagccaaaggcagccccgagaaccacaggtgtacacctgcccccatcccgaggagatgaccaagaaccaggtcagcctgacctgcc  
25 tgggtcaaaggcttctatccagcgcacatcgccgtggagtgaggagcaatgggcagccggagagaacaactacaagaccacgcctcccgtgctgg  
actccgacggctccttctctctacagcaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcatgctccgtgatgag  
gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 1460).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the  
30 polynucleotide sequence of SEQ ID NO: 1471 which encodes the light chain polypeptide sequence of  
SEQ ID NO: 1461 and which consists of the light chain variable region coding sequence of SEQ ID NO:  
1472 and the light chain constant region coding sequence of SEQ ID NO: 1480.

In another 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: 1462:

5 cagggtgctgacccagtcctctccaccctgtctgcatctgtaggagacagagtcaccatcacttgctcagtcagtgagtggttacggtaactact  
tagccttggtttcagcagaaaccaggaaaagccctaagttcctgatctatgaagcatcctaactggaatctggagtcctcatcaaggttcagcgg  
cagtggtatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaactactactgtgcaggcgggtatattagtgagg  
tggtgctttcggcggaggaaaccaaggtggaaatcaaact (SEQ ID NO: 1472).

10 In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 1470:

acggtagcggcccatctgtcttcatcttccgccatctgatgagcagttgaaatctggaactgcctctgttggtgcctgctgaataacttctatcc  
cagagaggccaaagtacagtggagggtgataacgccctcaatcggttaactccaggagagtggtcacagagcaggacagcaaggacagc  
acctacagcctcagcagcacctgacgctgagcaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcaggcctgagc  
15 tcgccgtcacaaagagcttcaacaggggagagtggt (SEQ ID NO: 1480).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1454; SEQ ID NO: 1456; and SEQ ID NO: 1458, which correspond to  
20 polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1441, or the variable heavy chain sequence of SEQ ID NO: 1442, and/or one or more of the polynucleotide sequences of SEQ ID NO: 1474; SEQ ID NO: 1476; and SEQ ID NO: 1478, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1461, or the variable light chain sequence of SEQ ID NO: 1462, or combinations of these polynucleotide sequences.

25 In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

30 In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1453; SEQ ID NO: 1455; SEQ ID NO: 1457; and SEQ ID NO: 1459, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1441, or the variable heavy chain sequence of SEQ ID NO: 1442, and/or one or more of the

polynucleotide sequences of SEQ ID NO: 1473; SEQ ID NO: 1475; SEQ ID NO: 1477; and SEQ ID NO: 1479, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1461, or the variable light chain sequence of SEQ ID NO: 1462, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of  
5 the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the  
10 polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1451 encoding the heavy chain sequence of SEQ ID NO: 1441; the polynucleotide SEQ ID NO: 1452 encoding the variable heavy chain  
15 sequence of SEQ ID NO: 1442; the polynucleotide SEQ ID NO: 1471 encoding the light chain sequence of SEQ ID NO: 1461; the polynucleotide SEQ ID NO: 1472 encoding the variable light chain sequence of SEQ ID NO: 1462; polynucleotides encoding the CDRs (SEQ ID NO: 1454; SEQ ID NO: 1456; and SEQ ID NO: 1458) of the heavy chain sequence of SEQ ID NO: 1441, or the variable heavy chain sequence of SEQ ID NO: 1442; polynucleotides encoding the CDRs (SEQ ID NO: 1474; SEQ ID NO: 1476; and SEQ  
20 ID NO: 1478) of the light chain sequence of SEQ ID NO: 1461, or the variable light chain sequence of SEQ ID NO: 1462; polynucleotides encoding the FRs (SEQ ID NO: 1453; SEQ ID NO: 1455; SEQ ID NO: 1457; and SEQ ID NO: 1459) of the heavy chain sequence of SEQ ID NO: 1441, or the variable heavy chain sequence of SEQ ID NO: 1442; and polynucleotides encoding the FRs (SEQ ID NO: 1473; SEQ ID NO: 1475; SEQ ID NO: 1477; and SEQ ID NO: 1479) of the light chain sequence of SEQ ID NO: 1461, or  
25 the variable light chain sequence of SEQ ID NO: 1462.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab10.H6, the polynucleotides encoding the full length Ab10.H6 antibody comprise, or  
30 alternatively consist of, the polynucleotide SEQ ID NO: 1451 encoding the heavy chain sequence of SEQ ID NO: 1441, and the polynucleotide SEQ ID NO: 1471 encoding the light chain sequence of SEQ ID NO: 1461.

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab10.H6 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab10.H6 or Fab fragments thereof, can be produced via expression of Ab10.H6 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 Ab21.H2

In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1491 which encodes the heavy chain sequence of SEQ ID NO: 1481 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1492 and the heavy chain constant region coding sequence of SEQ ID NO: 1500.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1482:

gaggtgcagcttgaggagctggggaggcttggtccagcctgggggtccctgagactctctgtgcagccttggaatcgacctcagtagcta  
ctacatgacctgggtccgtcaggctccagggaaggggctggagtggtcggattcattgatgctggtggtagcgatactacgcgacctgggca  
aaaggccgattcaccatctccagagacaattccaagaacaccgtgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattctg  
tgctagagatcttgacttggtggccaaggacacctgtcaccgtctcgagc (SEQ ID NO: 1492).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1490:

gcctccaccaaggcccatcggtcttccccctggcaccctctccaagagcacctctgggggcacagcgccctgggctgcctggtcaaggacta  
ctccccgaaccgggtgacgggtgctggaactcaggcgccctgaccagcggtgcacacctcccggctgtcctacagtcctcaggactctactc  
ctcagcagcgtggtgacctgacctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga  
caagaaagttgagcccaaatctgtgacaaaactcacacatgccaccgtgccagcacctgaactcctggggggaccgtcagttctctcttc

ccccaaaaccaaggacacctcatgatctccggaccctgaggtcacatgcgtgggtgggacgtgagccacgaagaccctgaggtcaagtt  
 caactgggtacgtggacggcgtggaggtgcataatgccaagacaaagccgaggaggagcagtagccagcacgtaccgtggtgagcgtcct  
 caccgtcctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagccccatcgagaaaaccatctc  
 caaagccaaagggcagccccgagaaccacaggtgtacacctgccccatccggaggagatgaccaagaaccaggtcagcctgacctgcc  
 5 tggtaaaggcttctatcccagcgatcgcgtggagtgaggagacaatgggcagccggagaacaactacaagaccacgcctcccgtgctgg  
 actccgacggctcttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
 gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 1500).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the  
 10 polynucleotide sequence of SEQ ID NO: 1511 which encodes the light chain polypeptide sequence of  
 SEQ ID NO: 1501 and which consists of the light chain variable region coding sequence of SEQ ID NO:  
 1512 and the light chain constant region coding sequence of SEQ ID NO: 1520.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
 15 consist of, the following polynucleotide sequence encoding the variable light chain polypeptide  
 sequence of SEQ ID NO: 1502:

gccgtgctgaccagctctctccaccctgtctgcatctgtaggagacagagtcaccatcacttgtaagtcagtgagagcgtttatgggtactact  
 tagcctggtttcagcagaaaccaggaaaagccccaagcaactgatctatgatgcatccactctggcatctggagtcaccaaggttcagcggc  
 agtggatctggaaacagaattcactctcaccatcagcagcctgagcctgatgatttgcacttactactgtgcaggcgggttatgttagtgaggt  
 20 gttgctttcggcggggaaccaagtggaatcaaact (SEQ ID NO: 1512).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
 consist of, the following polynucleotide sequence encoding the constant light chain polypeptide  
 sequence of SEQ ID NO: 1510:

acggtagcggccccatctgtcttcatcttccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtcctgctgaataacttctatcc  
 25 cagagaggccaaagtacagtggagggtggataacgccctcaatcgggtaactccaggagagtgatcacagagcaggacagcaaggacagc  
 acctacagcctcagcagccctgacgctgagcaagcagactacgagaaacacaaagtctacgctgcgaagtcacccatcaggcctgagc  
 tcgccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 1520).

30 In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
 binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
 sequences of SEQ ID NO: 1494; SEQ ID NO: 1496; and SEQ ID NO: 1498, which correspond to  
 polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO:  
 1481, or the variable heavy chain sequence of SEQ ID NO: 1482, and/or one or more of the



polynucleotide sequences of SEQ ID NO: 1514; SEQ ID NO: 1516; and SEQ ID NO: 1518, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1501, or the variable light chain sequence of SEQ ID NO: 1502, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1493; SEQ ID NO: 1495; SEQ ID NO: 1497; and SEQ ID NO: 1499, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1481, or the variable heavy chain sequence of SEQ ID NO: 1482, and/or one or more of the polynucleotide sequences of SEQ ID NO: 1513; SEQ ID NO: 1515; SEQ ID NO: 1517; and SEQ ID NO: 1519, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1501, or the variable light chain sequence of SEQ ID NO: 1502, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1491 encoding the heavy chain sequence of SEQ ID NO: 1481; the polynucleotide SEQ ID NO: 1492 encoding the variable heavy chain sequence of SEQ ID NO: 1482; the polynucleotide SEQ ID NO: 1511 encoding the light chain sequence of SEQ ID NO: 1501; the polynucleotide SEQ ID NO: 1512 encoding the variable light chain sequence of SEQ ID NO: 1502; polynucleotides encoding the CDRs (SEQ ID NO: 1494; SEQ ID NO: 1496; and SEQ ID NO: 1498) of the heavy chain sequence of SEQ ID NO: 1481, or the variable heavy chain sequence of SEQ ID NO: 1482; polynucleotides encoding the CDRs (SEQ ID NO: 1514; SEQ ID NO: 1516; and SEQ ID NO: 1518) of the light chain sequence of SEQ ID NO: 1501, or the variable light chain sequence of SEQ ID NO: 1502; polynucleotides encoding the FRs (SEQ ID NO: 1493; SEQ ID NO: 1495; SEQ ID NO:

1497; and SEQ ID NO: 1499) of the heavy chain sequence of SEQ ID NO: 1481, or the variable heavy chain sequence of SEQ ID NO: 1482; and polynucleotides encoding the FRs (SEQ ID NO: 1513; SEQ ID NO: 1515; SEQ ID NO: 1517; and SEQ ID NO: 1519) of the light chain sequence of SEQ ID NO: 1501, or the variable light chain sequence of SEQ ID NO: 1502.

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In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H2, the polynucleotides encoding the full length Ab21.H2 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 1491 encoding the heavy chain sequence of SEQ ID NO: 1481, and the polynucleotide SEQ ID NO: 1511 encoding the light chain sequence of SEQ ID NO: 1501.

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Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab21.H2 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab21.H2 or Fab fragments thereof, can be produced via expression of Ab21.H2 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*.

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### **Antibody Ab21.H3**

In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1531 which encodes the heavy chain sequence of SEQ ID NO: 1521 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1532 and the heavy chain constant region coding sequence of SEQ ID NO: 1540.

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In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1522:

gagggtgcagcttggagctctgggggaggcttggccagcctggggggtccctgagactctcctgtgcagcctctggaatcgacctcagtagcta  
ctacatgacctgggtccgtcaggctccagggaaggggctggagtgatcggttcattgatgctgggtgtagcgcatactacgcgacctgggca  
aaaggccgattcacatctccagagacaattccaagaacacgtgtatcttcaaataaacagcctgagagctgaggacactgctgtgtatttctg  
tgctagagatcttgactgtggggccaaggaccctctcaccgtctcgagc (SEQ ID NO: 1532).

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In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1530:

gcctccaccaaggcccatcggtcttcccctggcaccctcctcaagagcacctctgggggcacagcgccctgggctgcctgtcaaggacta  
10 cttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggtgcacaccttccggctgtcctacagtctcaggactctactc  
cctcagcagcgttggtgacctgtccctccagcagcttgggcacccagacatctgcaacgtgaatcacaagcccagcaaccaaggtgga  
caagaaagttgagcccaaatctgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctggggggaccgtcagttctcttcc  
ccccaaaaccgaaggacacctcatgatctccggaccctgaggtcacatgctgtgtggtggacgtgagccacgaagacctgagggtcaagtt  
caactgggtacgtggagcggtggaggtgcataatgccaagacaaagccggggaggagcagtagccagcacgtaccgtgtgtgagcgtctc  
15 caccgtcctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctccagccccatcgagaaaaccatctc  
caaagccaaaggcgagcccgagaaccacaggtgtacacctgccccatcccgaggagatgaccaagaaccaggtcagctgacctgcc  
tggtcaaaggcttctatcccagcgacatgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccagcctcccgtgtg  
actccgacggctccttctctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagagcctctcctgtctccgggtaaa (SEQ ID NO: 1540).

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In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1551 which encodes the light chain polypeptide sequence of SEQ ID NO: 1541 and which consists of the light chain variable region coding sequence of SEQ ID NO: 1552 and the light chain constant region coding sequence of SEQ ID NO: 1560.

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In another 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: 1542:

gacatccagctgaccagctctcctccaccctgtctgcatctgtaggagacagagtcacatcacttgtaagtcagtgagagcgttatggtgac  
30 tacttagcctggtttcagcagaaaccaggaaaagcccctaagcaactgatctatgatgcatccactctggcatctggagtcccatcaaggttcag  
cggcagtggtatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtgcaggcggtatgttagtgc  
aggtgttgccttcggcgagggaaccaaggtggaaatcaaacgt (SEQ ID NO: 1552).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 1550:

acggtagcggcccatctgtcttcatcttccgccatctgatgagcagttgaaatctggaactgcctctgttgctgctgaataacttctatcc  
5 cagagaggccaaagtacagtgggaaggtggataacgccctccaatcgggtaactcccaggagagtgacagagcaggacagcaaggacagc  
acctacagcctcagcagcaccctgacgtgagcaagcagactacgagaacacaaagtctacgcctgcgaagtcacccatcagggcctgagc  
tcgccgctcacaagagcttcaacaggggagagtggt (SEQ ID NO: 1560).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
10 binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 1534; SEQ ID NO: 1536; and SEQ ID NO: 1538, which correspond to  
polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO:  
1521, or the variable heavy chain sequence of SEQ ID NO: 1522, and/or one or more of the  
polynucleotide sequences of SEQ ID NO: 1554; SEQ ID NO: 1556; and SEQ ID NO: 1558, which  
15 correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1541, or the  
variable light chain sequence of SEQ ID NO: 1542, or combinations of these polynucleotide sequences.

In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention  
or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of  
polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain  
20 sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having  
binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide  
sequences of SEQ ID NO: 1533; SEQ ID NO: 1535; SEQ ID NO: 1537; and SEQ ID NO: 1539, which  
25 correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of  
SEQ ID NO: 1521, or the variable heavy chain sequence of SEQ ID NO: 1522, and/or one or more of the  
polynucleotide sequences of SEQ ID NO: 1553; SEQ ID NO: 1555; SEQ ID NO: 1557; and SEQ ID NO:  
1559, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1541,  
or the variable light chain sequence of SEQ ID NO: 1542, or combinations of these polynucleotide  
30 sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of  
the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more  
of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light  
chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides

5 encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1531 encoding the heavy chain sequence of SEQ ID NO: 1521; the polynucleotide SEQ ID NO: 1532 encoding the variable heavy chain sequence of SEQ ID NO: 1522; the polynucleotide SEQ ID NO: 1551 encoding the light chain sequence of SEQ ID NO: 1541; the polynucleotide SEQ ID NO: 1552 encoding the variable light chain sequence of SEQ ID NO: 1542; polynucleotides encoding the CDRs (SEQ ID NO: 1534; SEQ ID NO: 1536; and SEQ

10 ID NO: 1538) of the heavy chain sequence of SEQ ID NO: 1521, or the variable heavy chain sequence of SEQ ID NO: 1522; polynucleotides encoding the CDRs (SEQ ID NO: 1554; SEQ ID NO: 1556; and SEQ ID NO: 1558) of the light chain sequence of SEQ ID NO: 1541, or the variable light chain sequence of SEQ ID NO: 1542; polynucleotides encoding the FRs (SEQ ID NO: 1533; SEQ ID NO: 1535; SEQ ID NO: 1537; and SEQ ID NO: 1539) of the heavy chain sequence of SEQ ID NO: 1521, or the variable heavy

15 chain sequence of SEQ ID NO: 1522; and polynucleotides encoding the FRs (SEQ ID NO: 1553; SEQ ID NO: 1555; SEQ ID NO: 1557; and SEQ ID NO: 1559) of the light chain sequence of SEQ ID NO: 1541, or the variable light chain sequence of SEQ ID NO: 1542.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively

20 consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H3, the polynucleotides encoding the full length Ab21.H3 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 1531 encoding the heavy chain sequence of SEQ ID NO: 1521, and the polynucleotide SEQ ID NO: 1551 encoding the light chain sequence of SEQ ID NO: 1541.

25

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by

30 enzymatic digestion (e.g., papain) of Ab21.H3 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab21.H3 or Fab fragments thereof, can be produced via expression of Ab21.H3 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 Ab21.H4

- 5 In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to PACAP. In one embodiment, polynucleotides of the invention comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1571 which encodes the heavy chain sequence of SEQ ID NO: 1561 and which consists of the heavy chain variable region coding sequence of SEQ ID NO: 1572 and the heavy chain constant region coding sequence of
- 10 SEQ ID NO: 1580.

In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 1562:

- 15 gaggtgcagcttggagctctggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggaatcgacctcagtagcta  
ctacatgacctgggtccctcaggctccagggaagggtctggagtggatcggtcattgatgctggtgtagcgcatatacgcgacctgggca  
aaagccgattcaccatctccagagacaattccaagaacacacctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattctg  
tgctagagatcttgactgtggggccaaggacacctcgaccgtctcgagc (SEQ ID NO: 1572).

- 20 In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 1570:

- gcctccaccaagggccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcgccctgggctgcctggtcaaggacta  
cttccccgaaccgggtgacgggtgctggaactcaggcgccctgaccagcggtgcacaccttcccggctgtcctacagtctcaggacttactc  
25 cctcagcagcgtggtgacctgcccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaaccaagggtgga  
caagaaagttgagcccaaatctgtgacaaaactcacatgcccaccgtgcccagcacctgaactcctggggggaccgtcagttcttcttcc  
ccccaaaaccaaggacacctcatgatctccggaccctgaggtcacatgctggtggtggacgtgagccacgaagacctgaggtcaagtt  
caactggtacgtggacggcgtggaggtgcataatgccaagacaagccgaggaggagcagtagccagcacgtaccgtgtggtcagcgtcct  
caccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaagccctcccagccccatcgagaaaaccatctc  
30 caaagccaaagggcagccccgagaaccacaggtgtacacctgcccccatccggaggagatgaccaagaaccaggtcagcctgacctgcc  
tggtcaaaggcttctatccacgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgctcccgtgctgg  
actccgacggctcttcttctctacagcaagctcaccgtggacaagagcaggtggcagcagggaacgtcttctcatgctccgtgatgcatgag  
gctctgcacaaccactacacgcagaagagcctctcctgtctccgggtaaa (SEQ ID NO: 1580).

In another embodiment of the invention, polynucleotides comprise, or alternatively consist of, the polynucleotide sequence of SEQ ID NO: 1591 which encodes the light chain polypeptide sequence of SEQ ID NO: 1581 and which consists of the light chain variable region coding sequence of SEQ ID NO: 1592 and the light chain constant region coding sequence of SEQ ID NO: 1600.

5

In another 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: 1582:

gacatcgtgctgaccagtcctccacctgtctgcatctgtaggagacagagtcacatcacttgtaagtcagtgagagcggttatgggtgact  
10 acttagcctgggttcagcagaaaccaggaaaagccctaagcaactgatctatgatgcatccactctggcatctggagtcacatcaaggttcagc  
ggcagtggtatcggaaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaactactactgtgcaggcggttatgtagtgca  
ggtgttgctttcgcgaggagaaccaaggtggaatcaaact (SEQ ID NO: 1592).

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively  
15 consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 1590:

acggtagcgccccatctgtcttcattctccgccatctgatgagcagtgaaatctggaactgcctctgtgtgctgctgaataacttctatcc  
cagagaggccaaagtacagtgggaaggtggataacgccctccaatcgggtaactcccaggagagtgacagagcaggacagcaaggacagc  
acctacagcctcagcagcacctgacgctgagcaagcagactacgagaaacaaaagtctacgcctgcgaagtcacccatcaggcgctgagc  
20 tcgcccgtcacaaagagcttcaacaggggagagtggt (SEQ ID NO: 1600).

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1574; SEQ ID NO: 1576; and SEQ ID NO: 1578, which correspond to  
25 polynucleotides encoding the CDRs (hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1561, or the variable heavy chain sequence of SEQ ID NO: 1562, and/or one or more of the polynucleotide sequences of SEQ ID NO: 1594; SEQ ID NO: 1596; and SEQ ID NO: 1598, which correspond to the CDRs (hypervariable regions) of the light chain sequence of SEQ ID NO: 1581, or the variable light chain sequence of SEQ ID NO: 1582, or combinations of these polynucleotide sequences.

30 In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or antigen-binding fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

In a further embodiment of the invention, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 1573; SEQ ID NO: 1575; SEQ ID NO: 1577; and SEQ ID NO: 1579, which correspond to polynucleotides encoding the FRs (constant regions) of the heavy chain sequence of SEQ ID NO: 1561, or the variable heavy chain sequence of SEQ ID NO: 1562, and/or one or more of the polynucleotide sequences of SEQ ID NO: 1593; SEQ ID NO: 1595; SEQ ID NO: 1597; and SEQ ID NO: 1599, which correspond to the FRs (constant regions) of the light chain sequence of SEQ ID NO: 1581, or the variable light chain sequence of SEQ ID NO: 1582, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antigen-binding fragments described herein. In one embodiment, polynucleotides encoding antigen-binding fragments having binding specificity to PACAP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antigen-binding fragments: the polynucleotide SEQ ID NO: 1571 encoding the heavy chain sequence of SEQ ID NO: 1561; the polynucleotide SEQ ID NO: 1572 encoding the variable heavy chain sequence of SEQ ID NO: 1562; the polynucleotide SEQ ID NO: 1591 encoding the light chain sequence of SEQ ID NO: 1581; the polynucleotide SEQ ID NO: 1592 encoding the variable light chain sequence of SEQ ID NO: 1582; polynucleotides encoding the CDRs (SEQ ID NO: 1574; SEQ ID NO: 1576; and SEQ ID NO: 1578) of the heavy chain sequence of SEQ ID NO: 1561, or the variable heavy chain sequence of SEQ ID NO: 1562; polynucleotides encoding the CDRs (SEQ ID NO: 1594; SEQ ID NO: 1596; and SEQ ID NO: 1598) of the light chain sequence of SEQ ID NO: 1581, or the variable light chain sequence of SEQ ID NO: 1582; polynucleotides encoding the FRs (SEQ ID NO: 1573; SEQ ID NO: 1575; SEQ ID NO: 1577; and SEQ ID NO: 1579) of the heavy chain sequence of SEQ ID NO: 1561, or the variable heavy chain sequence of SEQ ID NO: 1562; and polynucleotides encoding the FRs (SEQ ID NO: 1593; SEQ ID NO: 1595; SEQ ID NO: 1597; and SEQ ID NO: 1599) of the light chain sequence of SEQ ID NO: 1581, or the variable light chain sequence of SEQ ID NO: 1582.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab fragments having binding specificity for PACAP. With respect to antibody Ab21.H4, the polynucleotides encoding the full length Ab21.H4 antibody comprise, or



alternatively consist of, the polynucleotide SEQ ID NO: 1571 encoding the heavy chain sequence of SEQ ID NO: 1561, and the polynucleotide SEQ ID NO: 1591 encoding the light chain sequence of SEQ ID NO: 1581.

- 5 Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, or HEK-293 cells, 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, Fab fragments can be produced by enzymatic digestion (e.g., papain) of Ab21.H4 following expression of the full-length polynucleotides
- 10 in a suitable host. In another embodiment of the invention, anti-PACAP antibodies, such as Ab21.H4 or Fab fragments thereof, can be produced via expression of Ab21.H4 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*.

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#### Embodiments

- E1.** An anti-Pituitary Adenylate Cyclase-Activating Polypeptide ("PACAP") antibody and/or antigen-binding fragment thereof for use in treating, ameliorating and/or preventing headache such as medication overuse headache (MOH), or pain, such as hyperalgesia, allodynia or opioid-induced pain.
- 20 **E2.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to embodiment E1**, wherein the pain is opioid-induced pain, such as opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).
- E3.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one**
- 25 **of the preceding embodiments**, wherein the opioid-induced pain is opioid-induced hyperalgesia (OIH) or opioid-induced allodynia (OIA).
- E4.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the opioid-induced pain is opioid-induced hyperalgesia (OIH).
- 30 **E5.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to embodiment 1 or 2**, wherein the opioid-induced pain is opioid-induced chronic migraine.
- E6.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use according to any one of the preceding embodiments, wherein the opioid-induced pain is resulting from treatment of the subject with an opioid analgesics selected from the group consisting of codeine, dihydrocodeine,

morphine or a morphine derivative or pharmaceutically acceptable salt thereof, codeine, dihydrocodeine, oxycodone, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanil, meperidine, methadone, nalbuphine, propoxyphene, and pentazocine, or pharmaceutically acceptable salts thereof.

5    **E7.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the opioid-induced pain is resulting from treatment of the subject with morphine.

10    **E8.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof antagonize, inhibit, neutralize, and/or block at least one biological effect associated with human PACAP.

15    **E9.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21, Ab21.H, Ab21.H2, Ab21.H3, or Ab21.H4.

20    **E10.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6.

25    **E11.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of an anti-PACAP antibody selected from Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6.

30    **E12.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H or Ab10.H3.

30    **E13.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H or Ab10.H3.

- E14.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H.
- 5 **E15.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H.
- E16.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one**  
 10 **of embodiments E1 to E13**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H3.
- E17.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one**  
 15 **of embodiments E1 to E13**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H3.
- E18.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one**  
**of embodiments E1 to E15**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises
- 20 a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 962 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 982 and comprising a CDR1 sequence consisting of
- 25 SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;
- b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 982;
- c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and (ii) a variable light  
 30 chain having the amino acid sequence of SEQ ID NO: 982;
- d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 961 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or

99% sequence identity to SEQ ID NO: 981 and comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;

5 e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 981; and/or

f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 981.

**E19.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of embodiments E1 to E13 or E16 to E17**, wherein the anti-PACAP antibody and/or antigen-binding  
10 fragment thereof comprises

a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1322 and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90,  
15 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1342 and comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;

b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1342;

20 c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1342;

d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1321 or 1604 and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96,  
25 97, 98, or 99% sequence identity to SEQ ID NO: 1341 and comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;

e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1341; and/or  
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f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 1341.

- E20.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is chimeric, human or humanized.
- E21.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is selected from the group consisting of scFvs, camelbodies, nanobodies, Immunoglobulin New Antigen Receptor ("IgNAR"), fragment antigen binding ("Fab") fragments, Fab' fragments, MetMab like antibodies, monovalent antigen-binding fragments, and F(ab')<sub>2</sub> fragments.
- E22.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof substantially or entirely lacks N-glycosylation and/or O-glycosylation.
- E23.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises a human constant domain; optionally wherein the antibody is an IgG1, IgG2, IgG3, or IgG4 antibody.
- E24.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation, optionally wherein the Fc region contains one or more mutations that alters or eliminates N- and/or O-glycosylation, and/or the Fc region comprises the sequence of any one of SEQ ID NO: 1244, 1245 or 1246.
- E25.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a binding affinity (KD) of less than or equal to  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M, or  $10^{-13}$  M, e.g., as determined by ELISA, bio-layer interferometry ("BLI"), KINEXA or surface plasmon resonance at 25° or 37°C.
- E26.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a binding affinity (KD) of less than or equal to  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M, or  $10^{-12}$  M.
- E27.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment

thereof binds to PACAP with an off-rate (kd) of less than or equal to  $5 \times 10^{-4} \text{ s}^{-1}$ ,  $10^{-4} \text{ s}^{-1}$ ,  $5 \times 10^{-5} \text{ s}^{-1}$ , or  $10^{-5} \text{ s}^{-1}$ .

**E28.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is directly or indirectly attached to a detectable label or therapeutic agent.

**E29.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a KD that is less than about 100 nM, 40 nM, 50 pM, 25pM, or is between about 10 pM and about 100 pM.

**E30.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof has stronger affinity for PACAP as compared to VIP and/or does not bind to VIP, optionally wherein the affinity of said antibody or antigen-binding fragment to PACAP is at least 10-fold, 30-fold, 100-fold, 300-fold, 1000-fold, 3000-fold, 10000-fold, 30000-fold, 100000-fold, 300000-fold, 1000000-fold, 3000000-fold, 10000000-fold, 30000000-fold or more stronger than the affinity of said antibody or antigen-binding fragment to VIP.

**E31.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is attached to at least one effector or functional moiety and/or one or more detectable moieties, e.g., a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixture thereof.

**E32.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues wherein said epitope is selected from the group consisting of:

- a. at least one of residues 22, 23, 27, 28, and 31 of a human PACAP;
- b. at least one of residues 12, 20, 23, 24, 26, 27, and 28 of a human PACAP;
- c. at least one of residues 19, 22, 23, and 27 of a human PACAP;
- d. at least two of the residues of (a), (b), or (c);
- e. at least three of the residues of (a), (b), or (c);
- f. at least four of the residues of (a), (b), or (c);
- g. at least five of the residues of (a) or (b);
- h. at least six of the residues of (b);
- i. at least seven of the residues of (b); and

j. at least the residues 23, 27, and 28, of a human PACAP, and optionally, between one to six of the additional residues of (a) and/or (b).

**E33.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof

a. specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues that is present in human wild-type PACAP38) but not human wild-type human PACAP27;

b. specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues, wherein said epitope consists of the residues of any one of (a) or (b) or (c) **as set forth in E32**; and/or

c. specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues) that is present in human wild-type PACAP38 and in human wild-type human PACAP27.

**E34.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof does not substantially interact with (bind) Vasoactive Intestinal Peptide ("VIP").

**E35.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises or elicits one of the following effects:

a. inhibits or neutralizes at least one biological effect elicited by PACAP;

b. neutralizes or inhibits PACAP activation of at least one of PAC1 receptor ("PAC1-R"), vasoactive intestinal peptide receptor type 1 ("VPAC1-R"), and/or vasoactive intestinal peptide receptor type 2 ("VPAC2-R");

c. neutralizes or inhibits PACAP activation of each of PAC1-R, VPAC1-R, and VPAC2-R;

d. neutralizes or inhibits PACAP activation of PAC1-R;

e. is capable of inhibiting PACAP binding to at least one of PAC1-R, VPAC1-R, and/or VPAC2-R;

f. is capable of inhibiting PACAP binding to each of PAC1-R, VPAC1-R, and/or VPAC2-R;

g. is capable of inhibiting PACAP binding to PAC1-R-expressing cells;

h. is capable of inhibiting PACAP binding to the cell surface, e.g., via a glycosaminoglycan ("GAG");

i. does not inhibit PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG;

j. inhibits PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG;

k. inhibits PACAP-induced cAMP production; and/or

I. when administered to a subject reduces PACAP-induced vasodilation, photophobia, mast cell degranulation and/or neuronal activation.

**E36.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is administered as an isolated nucleic acid sequence or nucleic acid sequences encoding said anti-PACAP antibody and/or antigen-binding fragment, or as a vector or vectors containing said isolated nucleic acid sequence or nucleic acid sequences.

**E37.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is administered as a host cell comprising the isolated nucleic acid sequence or sequences **or the vector or vectors of embodiment E36.**

**E38.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to embodiment E37**, wherein

a. said host cell is a mammalian, bacterial, fungal, yeast, avian, amphibian, plant or insect cell, or is a CHO cell, optionally:

(a) a filamentous fungus or a yeast, e.g., selected from the following genera: *Arxiozyma*; *Ascombotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*, preferably *Pichia*, and more preferably *Pichia pastoris*, *Pichia methanolica* or *Hansenula polymorpha* (*Pichia angusta*); or

(b) a mammalian cell, e.g., selected from the following: baby hamster kidney ("BHK") cells; Chinese hamster ovary ("CHO") cells; mouse Sertoli cells ("TM4" cells); African green monkey kidney cells ("VERO-76" cells); human cervical carcinoma ("HELA") cells; canine kidney cells ("MDCK"); buffalo rat liver ("BRL") cells; human lung cells; human liver ("Hep G2") cells; mouse mammary tumor ("MMT") cells; TRI cells; MRC 5 cells; and FS4 cells; and/or

b. said host cell is a CHO cell that is selected from one of the following subclones or sub-cell lines: DP12 (CHO K1 dhfr-) cell line, NS0 cells, CHO-DXB11 (CHO-DUKX), CHO-pro3, CHO-DG44, CHO 1-15, CHO DP-12, Lec2, M1WT3, Lec8, or pgsA-745.

**E39.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of the preceding embodiments**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered prior to the administration of an opioid.

**E40.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to E39**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered about one



week or 2 weeks prior to, or 6, 5, 4, 3, 2 or 1 day prior to, or 20, 16, 12, 8, 6, 4, 2 or 1 hour prior to the administration of an opioid.

**E41.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any one of embodiments E1 to E38**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered after the administration of an opioid.

**E42.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to embodiment E41**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered within about 1 hour, 6 hours, 12 hours, 1 day, 2 days, 4 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 8 months, 10 months or 1 year after the administration of an opioid.

**E43.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any of embodiments E1 to E38**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered concurrent to the administration of an opioid.

**E44.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any of the preceding embodiments**, which includes the administration of an anti-PACAP antibody and/or antigen-binding fragment and an opioid, and which combined administration elicits an additive or synergistic effect on ameliorating and/or preventing pain, such as hyperalgesia, allodynia or opioid-induced pain, optionally opioid-induced pain, optionally opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

**E45.** The anti-PACAP antibody and/or antigen-binding fragment thereof for use **according to any of the preceding embodiments**, wherein the subject has a prior or family history of opioid-induced pain, such as opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

**E46.** Use of an anti-Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) antibody and/or antigen-binding fragment thereof in the manufacture of a medicament for treating, ameliorating and/or preventing pain, such as hyperalgesia, allodynia or opioid-induced pain.

**E47.** The use **according to embodiment E46**, wherein the pain is opioid-induced pain, such as opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

**E48.** The use **according to any one of embodiments E46 to E47**, wherein the opioid-induced pain is opioid-induced hyperalgesia (OIH) or opioid-induced allodynia (OIA).

**E49.** The use **according to any one of any one of embodiments E46 to E48**, wherein the opioid-induced pain is opioid-induced hyperalgesia (OIH).

- E50.** The use **according to any one of embodiments E46 to E47**, wherein the opioid-induced pain is opioid-induced chronic migraine.
- E51.** The use **according to any one of embodiments E46 to E50**, wherein the opioid-induced pain is resulting from treatment of the subject with an opioid analgesics selected from the group consisting of codeine, dihydrocodeine, morphine or a morphine derivative or pharmaceutically acceptable salt thereof, codeine, dihydrocodeine, oxycodone, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanil, meperidine, methadone, nalbuphine, propoxyphene, and pentazocine, or pharmaceutically acceptable salts thereof.
- E52.** The use **according to any one of embodiments E46 to E51**, wherein the opioid-induced pain is resulting from treatment of the subject with morphine.
- E53.** The use **according to any one of embodiments E46 to E52**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof antagonize, inhibit, neutralize, and/or block at least one biological effect associated with human PACAP.
- E54.** The use **according to any one of embodiments E46 to E53**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21, Ab21.H, Ab21.H2, Ab21.H3, or Ab21.H4.
- E55.** The use **according to any one of embodiments E46 to E54**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6.
- E56.** The use **according to any one of embodiments E46 to E55**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of an anti-PACAP antibody selected from Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6.
- E57.** The use **according to any one of embodiments E46 to E56**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H or Ab10.H3.
- E58.** The use **according to any one of embodiments E46 to E57**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H or Ab10.H3.

- E59.** The use **according to any one of embodiments E46 to E58**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H.
- E60.** The use **according to any one of embodiments E46 to E59**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H.
- E61.** The use **according to any one of embodiments E46 to E58**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H3.
- E62.** The use **according to any one of embodiments E46 to E58**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H3.
- E63.** The use **according to any one of embodiments E46 to E60**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises
- a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 962 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 982 and comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;
  - b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 982;
  - c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 982;
  - d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 961 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 981 and comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;
  - e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 981; and/or

f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 981.

**E64.** The use **according to any one of embodiments E46 to E58 or E61 to E62**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises

- 5 a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1322 and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1342 and comprising a CDR1 sequence  
10 consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;
- b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1342;
- c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and (ii) a variable  
15 light chain having the amino acid sequence of SEQ ID NO: 1342;
- d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1321 or 1604 and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96,  
20 97, 98, or 99% sequence identity to SEQ ID NO: 1341 and comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;
- e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1341; and/or
- 25 f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 1341.

**E65.** The use **according to any one of embodiments E46 to E64**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is chimeric, human or humanized.

- E66.** The use **according to any one of embodiments E46 to E65**, wherein the anti-PACAP antibody  
30 and/or antigen-binding fragment thereof is selected from the group consisting of scFvs, camelbodies, nanobodies, Immunoglobulin New Antigen Receptor ("IgNAR"), fragment antigen binding ("Fab") fragments, Fab' fragments, MetMab like antibodies, monovalent antigen-binding fragments, and F(ab')<sub>2</sub> fragments.

- E67.** The use **according to any one of embodiments E46 to E66**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof substantially or entirely lacks N-glycosylation and/or O-glycosylation.
- E68.** The use **according to any one of embodiments E46 to E67**, wherein the anti-PACAP antibody  
5 and/or antigen-binding fragment thereof comprises a human constant domain; optionally wherein the antibody is an IgG1, IgG2, IgG3, or IgG4 antibody.
- E69.** The use **according to any one of embodiments E46 to E68**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation, optionally wherein the Fc region  
10 contains one or more mutations that alters or eliminates N- and/or O-glycosylation, and/or the Fc region comprises the sequence of any one of SEQ ID NO: 1244, 1245 or 1246.
- E70.** The use **according to any one of embodiments E46 to E69**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a binding affinity (KD) of less than or equal to  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M, or  $10^{-13}$  M, e.g., as determined by ELISA,  
15 bio-layer interferometry ("BLI"), KINEXA or surface plasmon resonance at 25° or 37°C.
- E71.** The use **according to any one of embodiments E46 to E70**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a binding affinity (KD) of less than or equal to  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M, or  $10^{-12}$  M.
- E72.** The use **according to any one of embodiments E46 to E71**, wherein the anti-PACAP antibody  
20 and/or antigen-binding fragment thereof binds to PACAP with an off-rate (kd) of less than or equal to  $5 \times 10^{-4}$  s<sup>-1</sup>,  $10^{-4}$  s<sup>-1</sup>,  $5 \times 10^{-5}$  s<sup>-1</sup>, or  $10^{-5}$  s<sup>-1</sup>.
- E73.** The use **according to any one of embodiments E46 to E72**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is directly or indirectly attached to a detectable label or  
25 therapeutic agent.
- E74.** The use **according to any one of embodiments E46 to E73**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a KD that is less than about 100 nM, 40 nM, 50 pM, 25pM, or is between about 10 pM and about 100 pM.
- E75.** The use **according to any one of embodiments E46 to E74**, wherein the anti-PACAP antibody  
30 and/or antigen-binding fragment thereof has stronger affinity for PACAP as compared to VIP and/or does not bind to VIP, optionally wherein the affinity of said antibody or antigen-binding fragment to PACAP is at least 10-fold, 30-fold, 100-fold, 300-fold, 1000-fold, 3000-fold, 10000-fold, 30000-fold, 100000-fold, 300000-fold, 1000000-fold, 3000000-fold, 10000000-fold, 30000000-fold or more stronger than the affinity of said antibody or antigen-binding fragment to VIP.

- E76.** The use **according to any one of embodiments E46 to E75**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is attached to at least one effector or functional moiety and/or one or more detectable moieties, e.g., a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixture thereof.
- 5 **E77.** The use **according to any one of embodiments E46 to E76**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues wherein said epitope is selected from the group consisting of:
- a. at least one of residues 22, 23, 27, 28, and 31 of a human PACAP;
  - 10 b. at least one of residues 12, 20, 23, 24, 26, 27, and 28 of a human PACAP;
  - c. at least one of residues 19, 22, 23, and 27 of a human PACAP;
  - d. at least two of the residues of (i), (ii), or (iii);
  - e. at least three of the residues of (i), (ii), or (iii);
  - f. at least four of the residues of (i), (ii), or (iii);
  - 15 g. at least five of the residues of (i) or (ii);
  - h. at least six of the residues of (ii);
  - i. at least seven of the residues of (ii); and
  - j. at least the residues 23, 27, and 28, of a human PACAP, and optionally, between one to six of the additional residues of (i) and/or (ii).
- 20 **E78.** The use **according to any one of embodiments E46 to E77**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof
- a. specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues that is present in human wild-type PACAP38) but not human wild-type human PACAP27;
  - 25 b. specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues, wherein said epitope consists of the residues of any one of (i) or (ii) or (iii) as set forth in Claim 21; and/or
  - c. specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues) that is present in human wild-type PACAP38 and in human wild-
  - 30 type human PACAP27.
- E79.** The use **according to any one of embodiments E46 to E78**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof does not substantially interact with (bind) Vasoactive Intestinal Peptide ("VIP").

- E80.** The use **according to any one of embodiments E46 to E79**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises or elicits one of the following effects:
- a. inhibits or neutralizes at least one biological effect elicited by PACAP;
  - b. neutralizes or inhibits PACAP activation of at least one of PAC1 receptor ("PAC1-R"), vasoactive intestinal peptide receptor type 1 ("VPAC1-R"), and/or vasoactive intestinal peptide receptor type 2 ("VPAC2-R");
  - c. neutralizes or inhibits PACAP activation of each of PAC1-R, VPAC1-R, and VPAC2-R;
  - d. neutralizes or inhibits PACAP activation of PAC1-R;
  - e. is capable of inhibiting PACAP binding to at least one of PAC1-R, VPAC1-R, and/or VPAC2-R;
  - 10 f. is capable of inhibiting PACAP binding to each of PAC1-R, VPAC1-R, and/or VPAC2-R;
  - g. is capable of inhibiting PACAP binding to PAC1-R-expressing cells;
  - h. is capable of inhibiting PACAP binding to the cell surface, e.g., via a glycosaminoglycan ("GAG");
  - i. does not inhibit PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG;
  - j. inhibits PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG;
  - 15 k. inhibits PACAP-induced cAMP production; and/or
  - l. when administered to a subject reduces PACAP-induced vasodilation, photophobia, mast cell degranulation and/or neuronal activation.
- E81.** The use **according to any one of embodiments E46 to E80**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is administered as an isolated nucleic acid sequence or
- 20 nucleic acid sequences encoding said anti-PACAP antibody and/or antigen-binding fragment, or as a vector or vectors containing said isolated nucleic acid sequence or nucleic acid sequences.
- E82.** The use **according to any one of embodiments E46 to E81**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is administered as a host cell comprising the isolated nucleic acid sequence or sequences or the vector or vectors of claim 38.
- 25 **E83.** The use **according to embodiment E82**, wherein
- a. said host cell is a mammalian, bacterial, fungal, yeast, avian, amphibian, plant or insect cell, or is a CHO cell, optionally:
    - (a) a filamentous fungus or a yeast, e.g., selected from the following genera: *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*, preferably *Pichia*, and more preferably *Pichia pastoris*, *Pichia methanolica* or *Hansenula polymorpha* (*Pichia angusta*); or
    - (b) a mammalian cell, e.g., selected from the following: baby hamster kidney ("BHK") cells; Chinese hamster ovary ("CHO") cells; mouse Sertoli cells ("TM4" cells); African green monkey kidney cells

("VERO-76" cells); human cervical carcinoma ("HELA") cells; canine kidney cells ("MDCK"); buffalo rat liver ("BRL") cells; human lung cells; human liver ("Hep G2") cells; mouse mammary tumor ("MMT") cells; TRI cells; MRC 5 cells; and FS4 cells; and/or

b. said host cell is a CHO cell that is selected from one of the following subclones or sub-cell lines:

- 5 DP12 (CHO K1 dhfr-) cell line, NS0 cells, CHO-DXB11 (CHO-DUKX), CHO-pro3, CHO-DG44, CHO 1-15, CHO DP-12, Lec2, M1WT3, Lec8, or pgsA-745.

**E84.** The use **according to any one of the preceding embodiments**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered prior to the administration of an opioid.

- 10 **E85.** The use **according to embodiment E84**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered about one week or 2 weeks prior to, or 6, 5, 4, 3, 2 or 1 day prior to, or 20, 16, 12, 8, 6, 4, 2 or 1 hour prior to the administration of an opioid.

**E86.** The use **according to any one of embodiments E46 to E83**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered after the administration of an opioid.

- 15 **E87.** The use **according to embodiment 86**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered within about 1 hour, 6 hours, 12 hours, 1 day, 2 days, 4 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 8 months, 10 months or 1 year after the administration of an opioid.

**E88.** The use **according to any of embodiments E46 to E83**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered concurrent to the administration of an opioid.

- 20 **E89.** The use **according to any of the preceding embodiments**, which includes the administration of an anti-PACAP antibody and/or antigen-binding fragment and an opioid, and which combined administration elicits an additive or synergistic effect on ameliorating and/or preventing pain, such as hyperalgesia, allodynia or opioid-induced pain, optionally opioid-induced pain, optionally opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

**E90.** The use **according to any of the preceding embodiments**, wherein the subject has a prior or family history of opioid-induced pain, such as opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).

- 30 **E91.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**.

**E92.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said medication overuse comprises use of ergotamine on 10 or more days/month, use of a triptan on 10 or more days/month,



use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as  
5 further described below) on 10 or more days/month, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

**E93.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse  
10 headache **according to any of the previous embodiments**, wherein said medication overuse headache comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse  
15 headache attributed to other medication, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone.

**E94.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse  
20 headache **according to any of the previous embodiments**, wherein said non-opioid analgesic-overuse headache comprises paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache, or other non-opioid analgesic-overuse headache.

**E95.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse  
25 headache **according to any of the previous embodiments**, wherein said ergotamine-overuse headache comprises headache occurring on 15 or more days/month and use of ergotamine on 10 or more days/month for more than 3 month.

**E96.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse  
headache **according to any of the previous embodiments**, wherein said triptan-overuse headache  
30 comprises headache occurring on 15 or more days/month and use of one or more triptans on 10 or more days/month for more than 3 months, wherein said triptan use optionally comprises use of one

or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan.

5     **E97.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said non-opioid analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

10     **E98.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache according to any of the previous embodiments, wherein said combination-analgesic-overuse headache comprises headache occurring on 15 or more days/month and use of one or more combination-analgesics on 10 or more days/month for more than 3 months, wherein said combination-analgesic comprises drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as  
15     tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

**E99.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said opioid-overuse headache comprises headache occurring on 15 or more days/month and use of one or more opioids (such as  
20     oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on 10 or more days/month for more than 3 months.

**E100.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said medication-overuse headache attributed to multiple drug classes not individually overused comprises headache occurring  
25     on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on a total of at least 10 days/month for more than 3 months.

30     **E101.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said medication-overuse

headache attributed to unspecified or unverified overuse of multiple drug classes comprises headache occurring on 15 or more days/month and use of any combination of ergotamine, triptans (such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, or any combination thereof), non-opioid analgesics and/or opioids (such as oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof) on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

**E102.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said medication-overuse headache attributed to other medication comprises headache occurring on 15 or more days/month and use of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

**E103.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said patient had a pre-existing primary headache prior to developing said medication overuse headache.

**E104.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein headache days and/or medication use days are determined by reporting by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

**E105.** The method, use or anti-PACAP antibody or fragments thereof for use in medication overuse headache **according to any of the previous embodiments**, wherein said medication-overuse headache is diagnosed according to the third edition of the International Classification of Headache Disorders, wherein said medication-overuse headache optionally comprises ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

30

## Examples

### Example 1 – Treatment of opioid-induced hyperalgesia

The aim of this examples was to investigate and demonstrate the therapeutic potential of an anti-PACAP antibody or an antigen-binding fragment thereof in the treatment of opioid-induced hyperalgesia. The therapeutic effect was compared with the effect of M65 (a PAC1 receptor antagonist, Moro O et al., "Functional characterization of structural alterations in the sequence of the vasodilatory peptide maxadilan yields a pituitary adenylate cyclase-activating peptide type 1 receptor-specific antagonist", *J Biol Chem.* 1999 Aug 13;274(33):23103–10) and Olcegepant (a CGRP receptor antagonist).

### Materials and Methods:

The experiment was performed in triplicated with n=4/group each time, resulting in data from a total of 12 mice/group. An equal number of male and female C57BL6/J mice were tested in each group. Mice were habituated to testing rack for 2 days prior to Day 1.

### *Ab10.H (Anti-PACAP antibody) sequence:*

HC:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDN  
NTVYLQMNSLRADTAVYFCARDLDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT  
SWNSGALTSGVHTFPAVLQSSGLYSLSSVTPVSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE  
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVL  
HQQDWLNGKEYCKKVSNAKALPAIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG  
QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 961)

LC:

DAQLTQSPSTLSASVGDRVTITCQSSSESVYGNLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTIS  
QPDDFATYYCAGGDISEGVAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA  
LQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 981)

### *HlgG control (hlgG control antibody) sequence:*

HC:

QVQLVQSGAEVKKPGASVKVSCQASGYRFSNFIHWVRQAPGQRFWMGWINPYNGNKEFSAKFQDRVFTFA  
DTSANTAYMELRSLRSADTAVYYCARVGPYSWDDSPQDNYYMDVWGKGTIVIVSSASTKGPSVFPLAPSSKSTSG  
GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPVSSSLGTQTYICNVNHKPSNTKVDKK  
VEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK

KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT  
CLVKGFPYSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSL  
SLSPG (SEQ ID NO: 1601)

LC:

- 5 EIVLTQSPGTLSLSPGERATFSCRSSHISRRVAWYQHKGQAPRLVIHGVSNRASGISDRFSGSGSGTDFTLTITRV  
EPEDFALYYCQVYGASSYTFGQGTKLERKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL  
QSGNSQESVTEQDSKSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1602)

*Von Frey testing (stimulus-evoked mechanical pain sensitivity testing):*

- 10 Mechanical threshold was measured by Von Frey testing prior to any administration on days 1, 3, 5,  
and 7; and post-drug administration on day 5 (**Figure 13**).

The cephalic threshold for response to stimulus-evoked mechanical pain sensitivity was measured  
according to the up-down method described by Chaplan et al. 1994 (Chaplan SR. "Quantitative  
assessment of tactile allodynia in the rat paw", *J Neurosci Methods* 53:55–63, 1994). Briefly, the mice  
15 were tested in 4 oz paper cups, to which they had been previously habituated for 1 hour over 2 days  
prior. The periorbital region caudal to the eyes near the midline was tested with a series of eight von  
Frey filaments (bending force ranging from 0.008 to 2 g). A response was defined as a shaking or  
ducking of the head, or vigorous grooming of the periorbital region following stimulation. The first  
filament tested was 0.4g. In the absence of a response, a heavier filament (up) was tried, and in the  
20 presence of a response, a lighter filament (down) was tested. This pattern was followed for a  
maximum of four filaments following the first response.

A schematic of the experimental setup is provided in **Figure 13**, and further specified here.

DAY 1: Baseline von Frey testing was measured, where after the six groups of four mice/group were  
25 created (VEH-VEH, MORPH-VEH, MORPH-Ab10.H, MORPH-HlgG control, MORPH-M65, MORPH-  
Olcegepant). Mice were injected SC with either morphine (20 mg/kg) or vehicle (VEH: 0.9% saline) at  
9 am & 5 pm (the groups of MORPH-VEH, MORPH-Ab10.H, MORPH-HlgG control, MORPH-M65,  
MORPH-Olcegepant received morphine. The VEH-VEH group received vehicle).

DAY 2: Mice were injected SC with either morphine (20 mg/kg) or VEH at 9 am & 5 pm (the groups of  
30 MORPH-VEH, MORPH-Ab10.H, MORPH-HlgG control, MORPH-M65, MORPH-Olcegepant received  
morphine. The VEH-VEH group received vehicle).

DAY 3: Baseline von Frey testing was measured, where after MORPH-Ab10.H and MORPH-HlgG control  
mice were injected with their respective Abs once (Ab10.H (anti-PACAP Ab) = 10 mg/kg IP; HlgG control  
(hlgG Control Ab) = 10 mg/kg IP). Mice were injected SC with either morphine (20 mg/kg) or Vehicle

(VEH: 0.9% saline) at 9 am & 5 pm (the groups of MORPH-VEH, MORPH-Ab10.H, MORPH-HlgG control, MORPH-M65, MORPH-Olcegepant received morphine. The VEH-VEH group received vehicle.

DAY 4: Mice were injected SC with either morphine (40 mg/kg) or Vehicle (VEH: 0.9% saline) at 9 am & 5 pm (the groups of MORPH-VEH, MORPH-Ab10.H, MORPH-HlgG control, MORPH-M65, MORPH-Olcegepant received morphine. The VEH-VEH group received vehicle).

DAY 5: Baseline von Frey testing was measured. After two hours, the MORPH-Olcegepant group of mice were administered Olcegepant (1 mg/kg IP). The VEH-VEH, MORPH-VEH, MORPH-Ab10.H, and MORPH-HlgG control were injected vehicle IP. 1.5 hours thereafter, the MORPH-M65 group of mice were administered M65 (0.1 mg/kg IP). 30 min thereafter, all groups were tested in von Frey test (the test was performed 4h following baseline assessment (2h post-Olcegepant; 30 min post-M65, 2 days post-Antibody).

DAY 7: Baseline von Frey testing was measured, where after tissue sample and blood samples were collected from the mice.

#### 15 Results:

A mouse model of OIH with robust opioid-induced hyperalgesia was established by chronic morphine (MORPH) administration.

Administration of anti-PACAP Ab provided full attenuation of the opioid-induced hyperalgesia when tested 2 days post administration (**Figures 14, 15, and 16**). In contrast, hlgG control Ab provided no relief. Acute administration of M65 was found to provide some relief when tested 30 min after drug administration (figure 15 and 16). Acute administration of Olcegepant was found to provide no significant relief when tested 2 hours after drug administration (Figure 15 and 16).

#### Conclusion:

25 The present example demonstrates that anti-PACAP antibodies significantly attenuated opioid-induced hyperalgesia in chronic morphine treated animals. Acute M65 also significantly attenuated opioid-induced hyperalgesia in chronic morphine treated animals. In contrast, inhibition of the CGRP pathway by acute administration of Olcegepant was found not to significantly attenuate opioid-induced hyperalgesia in chronic morphine treated animals.

30 In conclusion, the example demonstrates that administration of an anti-PACAP antibody provides treatment of opioid-induced pain.

#### **Example 2 – Treatment of opioid-induced chronic migraine**

The aim of this examples was to investigate and demonstrate the therapeutic potential of an anti-PACAP antibody or an antigen-binding fragment thereof in the treatment of opioid-induced chronic migraine, such as opioid-induced exacerbated migraine. The therapeutic effect was compared with the effect of M65 (a PAC1 receptor antagonist) and Olcegepant (a calcitonin gene-related peptide (CGRP) receptor antagonist).

#### Materials and methods:

The experiment was performed in 2X with n=4/group each time, resulting in data from a total of 8 mice/group. An equal number of male and female C57BL6/J mice were tested in each group. One of the morphine/NTG-M65 mice died on day 4 due to a faulty injection (pierced liver). Its data is excluded from the analysis. Mice were habituated to testing rack for 2 days prior to Day 1.

Once a day, mice were administered morphine, and every second day administered a low dose of nitroglycerin (NTG) which would not in itself trigger migraine.

#### *Ab10.H (Anti-PACAP antibody) sequence:*

HC:

EVQLVESGGGLVQPGGSLRLSCAASGIDLSYYMTWVRQAPGKGLEWIGFIDAGGDAYYASWAKGRFTISRDN  
NTVYLQMNSLRADTAVYFCARDLDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT  
SWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE  
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVL  
HQQDWLNGKEYKCKVSNKALPAPIEKTKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG  
QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 961)

LC:

DAQLTQSPSTLSASVGDRVTITCQSSSEVYGNLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTIS  
QPDDFATYYCAGGDISEGVAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA  
LQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 981)

#### *HlgG control (hlgG control antibody) sequence:*

HC:

QVQLVQSGAEVKKPGASVKVSCQASGYRFSNFIHWVRQAPGQRFWMGWINPYNGNKEFSAKFQDRVFTFA  
DTSANTAYMELRSLRSADTAVYYCARVGPYSWDDSPQDNYYMDVWGKGTIVIVSSASTKGPSVFPLAPSSKSTSG  
GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTQTYICNVNHKPSNTKVDKK  
VEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK

KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT  
CLVKGFPYSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVVFSCSVMHLEAHNHYTQKSL  
SLSPG (SEQ ID NO: 1601)

LC:

- 5 EIVLTQSPGTLSPGERATFSCRSSHISRRVAWYQHKGQAPRLVIHGVSNRASGISDRFSGSGSGTDFTLTITRV  
EPEDFALYYCQVYGASSYTFGQGTKLERKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL  
QSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC (SEQ ID NO: 1602)

*Von Frey testing (stimulus-evoked mechanical pain sensitivity testing):*

- 10 Mechanical threshold was measured by Von Frey testing prior to any administration on days 1, 3, 7,  
11, 12, and 14; and post-drug administration on day 12 (**Figure 17**).

The cephalic threshold for response to stimulus-evoked mechanical pain sensitivity was measured according to the up-down method described by Chaplan et al. 1994 (Chaplan SR. "Quantitative assessment of tactile allodynia in the rat paw", *J Neurosci Methods* 53:55–63, 1994), and elsewhere

- 15 (Aissa et al, "Soluble guanylyl cyclase is a critical regulator of migraine-associated pain", *Cephalgia*  
38(8): 1471-1484 2018, Anapindi et al, "PACAP and Other Neuropeptide Targets Link Chronic Migraine  
and Opioid-induced Hyperalgesia in Mouse Models", *Mol Cell Proteomics*, 18(12): 2447-2458, 2019,  
and Moye et al., "Delta opioid receptor agonists are effective for multiple types of headache  
disorders", *Neuropharmacology*, 148: 77-86, 2019). Briefly, the mice were tested in 4 oz paper cups,  
20 to which they had been previously habituated for 1 hour over 2 days prior. The periorbital region  
caudal to the eyes near the midline was tested with a series of eight von Frey filaments (bending force  
ranging from 0.008 to 2 g). A response was defined as a shaking or ducking of the head, or vigorous  
grooming of the periorbital region following stimulation. The first filament tested was 0.4g. In the  
absence of a response, a heavier filament (up) was tried, and in the presence of a response, a lighter  
25 filament (down) was tested. This pattern was followed for a maximum of four filaments following the  
first response.

A schematic of the experimental setup is provided in **Figure 17**. As specified below, once a day, mice  
were administered morphine, and every second day administered a low dose of nitroglycerin (NTG)  
30 which would not in itself trigger migraine.

DAY 1: Baseline von Frey testing was measured, where after the six groups of four mice/group were  
created (VEH-VEH, MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65,  
MOR/NTG-Olcegepant). Mice were injected SC with either morphine (10 mg/kg) or Vehicle (VEH: 0.9%



- saline) at 11 am (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle).
- DAY 2: Mice were injected SC with either morphine (10 mg/kg) or VEH at 11 am (the groups MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle).
- 5 DAY 3: Baseline von Frey testing was measured, where after at 11 am the mice were injected SC with either morphine (10 mg/kg) or Vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle) and IP with either nitroglycerin (NTG) (0.01 mg/kg) or vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received NTG. The VEH-VEH group received vehicle).
- 10 DAY 4: Mice were injected SC with either morphine (10 mg/kg) or VEH at 11 am (the groups MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle).
- 15 DAY 5: Mice were injected SC with either morphine (10 mg/kg) or Vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle) and IP with either nitroglycerin (NTG) (0.01 mg/kg) or vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received NTG. The VEH-VEH group received vehicle) at 11 am.
- 20 DAY 6: Mice were injected SC with either morphine (10 mg/kg) or VEH at 11 am (the groups MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle).
- DAY 7: Baseline von Frey testing was measured, where after at 11 am the mice were injected SC with either morphine (10 mg/kg) or Vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle) and IP with either nitroglycerin (NTG) (0.01 mg/kg) or vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received NTG. The VEH-VEH group received vehicle).
- 25 DAY 8: Mice were injected SC with either morphine (10 mg/kg) or VEH at 11 am (the groups MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle).
- 30 DAY 9: Mice were injected SC with either morphine (10 mg/kg) or Vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-

Olcegepant received morphine. The VEH-VEH group received vehicle) and IP with either nitroglycerin (NTG) (0.01 mg/kg) or vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received NTG. The VEH-VEH group received vehicle) at 11 am.

- 5 DAY 10: The MOR/NTG-Ab10.H and MOR/NTG-HlgG control mice were injected with their respective Antibodies once (Ab10.H (anti-PACAP Ab) = 10 mg/kg IP; HlgG control (hlgG Control Ab) = 10 mg/kg IP). Mice were injected SC with either morphine (10 mg/kg) or VEH at 11 am (the groups MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle).
- 10 DAY 11: Baseline von Frey testing was measured, where after at 11 am the mice were injected SC with either morphine (10 mg/kg) or Vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received morphine. The VEH-VEH group received vehicle) and IP with either nitroglycerin (NTG) (0.01 mg/kg) or vehicle (VEH: 0.9% saline) (the groups of MOR/NTG-VEH, MOR/NTG-Ab10.H, MOR/NTG-HlgG control, MOR/NTG-M65, MOR/NTG-Olcegepant received NTG. The VEH-VEH group received vehicle).
- 15 DAY 12: Baseline von Frey testing was measured. After two hours, the MOR/NTG-Olcegepant group of mice were administered Olcegepant (1 mg/kg IP). The VEH-VEH, MOR/NTG-VEH, MOR/NTG-Ab10.H, and MOR/NTG-HlgG control were injected vehicle IP. 1,5 hours thereafter, the MOR/NTG-M65 group of mice were administered M65 (0.1 mg/kg IP). 30 min thereafter, all groups were tested
- 20 in von Frey test (the test was performed 4h following baseline assessment (2h post-Olcegepant; 30 min post-M65, 2 days post-anti-PACAP Ab).
- DAY 14: Baseline von Frey testing was measured, where after tissue sample and blood samples were collected from the mice.

## 25 Results:

- A mouse model of opioid-induced chronic migraine was established by chronic morphine (MORPH) administration, followed by administration of intermittent low doses of nitroglycerin (NTG) which would not in itself trigger a migraine-related sensory response (**Figure 18**). Animals were treated with either hlgG control (HlgG control), Ab10.H (anti-PACAP mAb), acute Olcegepant (CGRP receptor
- 30 antagonist) or acute M65 (PAC1r antagonist).

Treatment with Ab10.H (anti-PACAP mAb) was found to significantly attenuate hyperalgesia related to opioid-induced chronic migraine in mice (**Figures 18, 19, 20, and 21**). In contrast, hlgG control Ab provided no relief. Acute administration of M65 was found also to provide some relief when tested 30

min after drug administration (**Figures 19, 20, 21**) Acute administration of Olcegepant was found to provide no significant relief when tested 2 hours after drug administration (**Figures 19, 20, and 21**).

Conclusion:

- 5 The present example demonstrates that PACAP/PAC1 signaling pathway blockade inhibits the opioid-induced chronic migraine in mice. Acute M65 also significantly attenuated the opioid-induced chronic migraine. In contrast, inhibition of the CGRP signaling pathway by acute administration of Olcegepant was found not to significantly attenuate the opioid-induced chronic migraine.
- 10 In conclusion, the example demonstrates that administration of an anti-PACAP antibody provides treatment of opioid-induced pain.

**Example 3 – Preventive Treatment of Opioid Induced Hyperalgesia (OIH)**

In the same model as used in Example 1, the preventive treatment with 20 mg/kg of PACAP antibody was tested and shown to effectively prevent the development of opioid induced hyperalgesia (OIH).

- 15 At this dose the antibody was effective as shown in **Figure 22**.

This experiment was performed over 3 cohorts.

- Each cohort had 24 male and female C57BL6J mice (equal number). Mice were purchased from JAX and were habituated to the colony for at least 1 week before testing began. Mice had enrichment (huts and chew sticks) placed in their cages 5 days before the first behaviour. They had cephalic baselines taken, grouped, and treated with 20 mg/kg Antibodies (IP) or vehicle saline. On day 2, baselines were taken, and they received twice daily escalating doses of morphine (20 mg/kg days 1-3, 40 mg/kg day 4 SC). Thresholds taken on day 2, 4, and 6. On day 6, 2h after baselines all mice were injected with vehicle (saline IP) or M65 (0.1 mg/kg) or olcegepant (1% DMSO 1 mg/kg). Mice were tested 2h post-olcegepant/Veh and 30 min post-M65. Plasma was collected on day 8 with trunk blood placed in K3EDTA tubes, with 10 microliter/millilitre DPP4, centrifuged, supernatant collected and stored at -80C. The experimenter was blinded to the conditions. n=10-11/group
- 20
- 25

Results are shown in **Figure 22**. Mechanical responses were determined in the cephalic/periorbital area using manual von Frey hair stimulation (up/down method starting with 0.4 g fiber).

30

**Example 4 – Preventive Treatment of Opioid Induced Migraine**

Opioid exacerbated migraine model/mixed morphine-NTG model – mice are treated with vehicle (veh) or 10 mg/kg SC morphine (mor) daily for 11 days. On days 3, 5, 7, 9, and 11 they are also treated with vehicle/NTG (0.01 mg/kg IP). In previous experiment (Example 2) we wanted to determine if PACAP

Ab could block established cephalic allodynia in this model. Mice were treated with PACAP or control antibody on day 10 of this paradigm. For this experiment (example 4) we wanted to determine if pre-treatment with PACAP antibody could prevent the establishment of cephalic allodynia to chronic morphine. In this case mice were given antibodies on day 2 of the morphine paradigm (the day before NTG administration began).

In the same model as used in Example 2, the preventive treatment with 20 mg/kg of PACAP antibody was tested and shown to effectively prevent the development of opioid induced headache as a model for medication overuse headache (MOH). The below experiment suggests that PACAP targeting therapies could be effective for the treatment of *i.a.* opioid exacerbated pain states.

The animals were divided into the following groups:

1. Vehichel (Veh) – Vehicle (Veh)
2. Morphine (MOR)/NTG-Veh
3. MOR/NTG-CTL AB
4. MOR/NTG-PACAP AB
5. MOR/NTG-Olcegepant
6. MOR/NTG-M65

Drugs administered

\* Veh=0.9% Saline--SC & IP

\* Morphine (MOR)= 10mg/kg --SC

\* NTG = 0.01 mg/kg--IP

\* Control antibody = 20mg/kg--IP

\* PACAP antibody = 20mg/kg--IP

\* Olcegepant= 1mg/kg --IP - vehicle is 1% DMSO/saline

\* M65=0.1 mg/kg --IP

Drug injection Schedule:

Antibodies injection only once at day 2.

Veh, MOR injection every day for 11 days.

NTG injection every other day, started at day 3 (Days 3,5,7,9,11).

Day 12 - mice tested acutely with IP vehicle, olcegepant, or M65.

Behavior tests of baseline schedule:

Before day 1 of the model, animals were habituated 2 times for 2 hr/time.

On Days 1, 3, 7, 12 and 14: Take measurements of the sensory responses at baseline before injections.

5 Day 1:

1. Take measurements of the sensory responses at baseline
2. Create the 6 groups (although until day 3 mice only get MOR or Veh)
3. Inject mice SC with either MOR (10mg/kg SC every day) or Veh at 11 AM

10 Day 2:

1. Antibodies injection
2. Inject mice SC with either MOR or Veh.

Day 12:

- 15 1. Take measurements of the sensory responses at baseline
2. Wait 2 hours and then inject with Olcegepant for group #5, inject other 5 groups (1, 2, 3, 4) with Veh;
3. Wait 1.5 hours after first injection and then inject with M65 IP for group #6;
4. 30 min after M65 injection, behaviour test all the groups.

20

Day 13:

Do nothing

Day 14:

- 25 Take blood, and centrifuge at 4 degree, take supernatants and store it in -80 degree.

Mechanical responses were determined in the cephalic/periorbital area using manual von Frey hair stimulation (up/down method starting with 0.4 g fiber). Mice were tested 1 day after the final morphine/NTG (day 12 mixed model) day with control acute treatments: PAC1 inhibitor M65 (0.1mg/kg IP) or olcegepant (1 mg/kg IP). On these test days basal responses were taken in the AM, 2h later mice were injected with olcegepant or vehicle and 1.5h later the M65 group was injected with M65. Mice were tested 30 minutes after that (i.e. 2h post-olcegepant and 30 min post-M65).

Results are shown in **Figure 23** and **24**.

## Claims

1. A method of treating, ameliorating and/or preventing medication overuse headache or pain, such as hyperalgesia, allodynia or opioid-induced pain, wherein the method comprises administering to a subject in need thereof an effective amount of an anti-Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) antibody.  
5
2. The method **according to claim 1**, wherein the pain is opioid-induced pain, such as opioid-induced pain selected from the group consisting of opioid-induced migraine e.g. opioid induced chronic or episodic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).  
10
3. The method **according to claims 1 or 2**, wherein the opioid-induced pain is opioid-induced hyperalgesia (OIH) or opioid-induced allodynia (OIA).
- 15 4. The method **according to any one of the preceding claims**, wherein the opioid-induced pain is opioid-induced hyperalgesia (OIH).
5. The method **according to claim 1 or 2**, wherein the opioid-induced pain is opioid-induced chronic migraine.  
20
6. The method **according to any one of the preceding claims**, wherein the opioid-induced pain is resulting from treatment of the subject with an opioid analgesics selected from the group consisting of codeine, dihydrocodeine, morphine or a morphine derivative or pharmaceutically acceptable salt thereof, codeine, dihydrocodeine, oxycodone, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene, and pentazocine, or pharmaceutically acceptable salts thereof.  
25
7. The method according to **any one of the preceding claims**, wherein the opioid-induced pain is resulting from treatment of the subject with morphine.  
30
8. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof antagonizes, inhibits, neutralizes, and/or blocks at least one biological effect associated with human PACAP.

9. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, Ab10.H6, Ab21, Ab21.H, Ab21.H2, Ab21.H3, or Ab21.H4.
10. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6.
11. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of an anti-PACAP antibody selected from Ab10.H, Ab10.H2, Ab10.H3, Ab10.H4, Ab10.H5, or Ab10.H6.
12. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H or Ab10.H3.
13. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H or Ab10.H3.
14. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H.
15. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H.

16. The method according to **any one of claims 1 to 13**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to the same or overlapping linear or conformational epitope(s) on human PACAP as Ab10.H3.
- 5 17. The method according to **any one of claims 1 to 13**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions ("CDRs") of the anti-PACAP antibody Ab10.H3.
- 10 18. The method according to **any one of claims 1 to 15**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises
- a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 962 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 982 and comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;
  - 15 b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 982;
  - 20 c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 962, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 982;
  - d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 961 and comprising a CDR1 sequence consisting of SEQ ID NO: 964; a CDR2 sequence consisting of SEQ ID NO: 966; and a CDR3 sequence consisting of SEQ ID NO: 968; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 981 and comprising a CDR1 sequence consisting of SEQ ID NO: 984; a CDR2 sequence consisting of SEQ ID NO: 986; and a CDR3 sequence consisting of SEQ ID NO: 988;
  - 25 e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 981; and/or
  - 30 f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 961, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 981.



19. The method according to **any one of claims 1 to 13 or 16 to 17**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises
- a. (i) a variable heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1322 and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a variable light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1342 and comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;
  - b. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and/or (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1342;
  - c. (i) a variable heavy chain having the amino acid sequence of SEQ ID NO: 1322, and (ii) a variable light chain having the amino acid sequence of SEQ ID NO: 1342;
  - d. (i) a heavy chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1321 or 1604 and comprising a CDR1 sequence consisting of SEQ ID NO: 1324; a CDR2 sequence consisting of SEQ ID NO: 1326; and a CDR3 sequence consisting of SEQ ID NO: 1328; and/or (ii) a light chain comprising an amino acid sequence with at least 80, 85, 90, 95, 96, 97, 98, or 99% sequence identity to SEQ ID NO: 1341 and comprising a CDR1 sequence consisting of SEQ ID NO: 1344; a CDR2 sequence consisting of SEQ ID NO: 1346; and a CDR3 sequence consisting of SEQ ID NO: 1348;
  - e. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and/or (ii) a light chain having the amino acid sequence of SEQ ID NO: 1341; and/or
  - f. (i) a heavy chain having the amino acid sequence of SEQ ID NO: 1321 or 1604, and (ii) a light chain having the amino acid sequence of SEQ ID NO: 1341.
20. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is chimeric, human or humanized.
21. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is selected from the group consisting of scFvs, camelbodies, nanobodies, Immunoglobulin New Antigen Receptor ("IgNAR"), fragment

antigen binding ("Fab") fragments, Fab' fragments, MetMab like antibodies, monovalent antigen-binding fragments, and F(ab')<sub>2</sub> fragments.

- 5           22. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof substantially or entirely lacks N-glycosylation and/or O-glycosylation.
- 10           23. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises a human constant domain; optionally wherein the antibody is an IgG1, IgG2, IgG3, or IgG4 antibody.
- 15           24. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation, optionally wherein the Fc region contains one or more mutations that alters or eliminates N- and/or O-glycosylation, and/or the Fc region comprises the sequence of any one of SEQ ID NO: 1244, 1245 or 1246.
- 20           25. The method according to **any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a binding affinity ( $K_D$ ) of less than or equal to  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M, or  $10^{-13}$  M, e.g., as determined by ELISA, bio-layer interferometry ("BLI"), KINEXA or surface plasmon resonance at 25° or 37°C.
- 25           26. The method according to any one of the preceding claims, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a binding affinity ( $K_D$ ) of less than or equal to  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M, or  $10^{-12}$  M.
- 30           27. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with an off-rate ( $k_d$ ) of less than or equal to  $5 \times 10^{-4}$  s<sup>-1</sup>,  $10^{-4}$  s<sup>-1</sup>,  $5 \times 10^{-5}$  s<sup>-1</sup>, or  $10^{-5}$  s<sup>-1</sup>.

28. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is directly or indirectly attached to a detectable label or therapeutic agent.
- 5 29. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof binds to PACAP with a  $K_D$  that is less than about 100 nM, 40 nM, 50 pM, 25pM, or is between about 10 pM and about 100 pM.
- 10 30. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof has stronger affinity for PACAP as compared to VIP and/or does not bind to VIP, optionally wherein the affinity of said antibody or antigen-binding fragment to PACAP is at least 10-fold, 30-fold, 100-fold, 300-fold, 1000-fold, 3000-fold, 10000-fold, 30000-fold, 100000-fold, 300000-fold, 1000000-fold, 3000000-fold, 10000000-fold, 30000000-fold or more stronger than the affinity of said antibody or antigen-binding fragment to VIP.
- 15 31. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is attached to at least one effector or functional moiety and/or one or more detectable moieties, e.g., a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixture thereof.
- 20 32. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues wherein said epitope is selected from the group consisting of:
- 25 a. at least one of residues 22, 23, 27, 28, and 31 of a human PACAP;  
b. at least one of residues 12, 20, 23, 24, 26, 27, and 28 of a human PACAP;  
c. at least one of residues 19, 22, 23, and 27 of a human PACAP;  
d. at least two of the residues of (a), (b), or (c);  
30 e. at least three of the residues of (a), (b), or (c);  
f. at least four of the residues of (a), (b), or (c);  
g. at least five of the residues of (a) or (b);  
h. at least six of the residues of (b);  
i. at least seven of the residues of (b); and

- j. at least the residues 23, 27, and 28, of a human PACAP, and optionally, between one to six of the additional residues of (a) and/or (b).

33. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody  
 5 and/or antigen-binding fragment thereof
- a. specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues that is present in human wild-type PACAP38) but not human wild-type human PACAP27;
  - 10 b. specifically binds to an epitope on human PACAP or a fragment or variant thereof containing the corresponding amino acid residues, wherein said epitope consists of the residues of any one of (a) or (b) or (c) **as set forth in Claim 32**; and/or
  - c. specifically binds to an epitope on human PACAP (or a fragment or variant thereof containing the corresponding amino acid residues) that is present in human wild-type PACAP38 and in human wild-type human PACAP27.
- 15
34. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof does not substantially interact with (bind) Vasoactive Intestinal Peptide ("VIP").
- 20
35. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof comprises or elicits one of the following effects:
- a. inhibits or neutralizes at least one biological effect elicited by PACAP;
  - b. neutralizes or inhibits PACAP activation of at least one of PAC1 receptor ("PAC1-R"), vasoactive intestinal peptide receptor type 1 ("VPAC1-R"), and/or vasoactive  
 25 intestinal peptide receptor type 2 ("VPAC2-R");
  - c. neutralizes or inhibits PACAP activation of each of PAC1-R, VPAC1-R, and VPAC2-R;
  - d. neutralizes or inhibits PACAP activation of PAC1-R;
  - e. is capable of inhibiting PACAP binding to at least one of PAC1-R, VPAC1-R, and/or VPAC2-R;
  - 30 f. is capable of inhibiting PACAP binding to each of PAC1-R, VPAC1-R, and/or VPAC2-R;
  - g. is capable of inhibiting PACAP binding to PAC1-R-expressing cells;
  - h. is capable of inhibiting PACAP binding to the cell surface, e.g., via a glycosaminoglycan ("GAG");

- i. does not inhibit PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG;
- j. inhibits PACAP-mediated binding of such antibody to the cell surface, e.g., via a GAG;
- k. inhibits PACAP-induced cAMP production; and/or
- 5 l. when administered to a subject reduces PACAP-induced vasodilation, photophobia, mast cell degranulation and/or neuronal activation.

36. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is administered as an isolated nucleic acid sequence or nucleic acid sequences encoding said anti-PACAP antibody and/or antigen-binding fragment, or as a vector or vectors containing said isolated nucleic acid sequence or nucleic acid sequences.

37. The method **according to any one of the preceding claims**, wherein the anti-PACAP antibody and/or antigen-binding fragment thereof is administered as a host cell comprising the isolated nucleic acid sequence or sequences or the vector or vectors **of claim 36**.

38. The method **according to claim 37**, wherein

- a. said host cell is a mammalian, bacterial, fungal, yeast, avian, amphibian, plant or insect cell, or is a CHO cell, optionally:

- (a) a filamentous fungus or a yeast, e.g., selected from the following genera: *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*, preferably *Pichia*, and more preferably *Pichia pastoris*, *Pichia methanolica* or *Hansenula polymorpha* (*Pichia angusta*); or

- (b) a mammalian cell, e.g., selected from the following: baby hamster kidney ("BHK") cells; Chinese hamster ovary ("CHO") cells; mouse Sertoli cells ("TM4" cells); African green monkey kidney cells ("VERO-76" cells); human cervical carcinoma ("HELA") cells; canine kidney cells ("MDCK"); buffalo rat liver ("BRL") cells; human lung cells; human liver ("Hep G2") cells; mouse mammary tumor ("MMT") cells; TRI cells; MRC 5 cells; and FS4 cells; and/or

- b. said host cell is a CHO cell that is selected from one of the following subclones or sub-cell lines: DP12 (CHO K1 dhfr-) cell line, NSO cells, CHO-DXB11 (CHO-DUKX), CHO-pro3, CHO-DG44, CHO 1-15, CHO DP-12, Lec2, M1WT3, Lec8, or pgsA-745.
39. The method **according to any one of the preceding claims**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered prior to the administration of an opioid.
40. The method **according to claim 39**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered about one week or 2 weeks prior to, or 6, 5, 4, 3, 2 or 1 day prior to, or 20, 16, 12, 8, 6, 4, 2 or 1 hour prior to the administration of an opioid.
41. The method **according to any one of claims 1 to 38**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered after the administration of an opioid.
42. The method **according to claim 41**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered within about 1 hour, 6 hours, 12 hours, 1 day, 2 days, 4 days, 6 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 8 months, 10 months or 1 year after the administration of an opioid.
43. The method according to **any of claims 1 to 38**, wherein said anti-PACAP antibody and/or antigen-binding fragment thereof is administered concurrent to the administration of an opioid.
44. The method according to **any of the preceding claims**, which includes the administration of an anti-PACAP antibody and/or antigen-binding fragment and an opioid, and which combined administration elicits an additive or synergistic effect on ameliorating and/or preventing pain, such as hyperalgesia, allodynia or opioid-induced pain, optionally opioid-induced pain, optionally opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).
45. The method **according to any of the preceding claims**, wherein the subject has a prior or family history of opioid-induced pain, such as opioid-induced pain selected from the group consisting of opioid-induced chronic migraine, opioid-induced hyperalgesia (OIH), and opioid-induced allodynia (OIA).