CLAIMS

1. An anti- pituitary adenylate-cyclase-activating polypeptide (PACAP) antibody, wherein:

(i) said antibody comprises heavy chain variable region (VH)-CDR1, VH-CDR2, and VH-CDR3 sequences set forth in SEQ ID NO: 9, 2, and 3, respectively; and light chain variable region (VL)-CDR1, VL-CDR2, and VL-CDR3 sequence set forth in SEQ ID NO: 10, 5, and 6, respectively;

(ii) said antibody or antigen-binding fragment thereof comprises VH-CDR1, VH-CDR2, and VH-CDR3 sequences selected from the group consisting of:

a) SEQ ID NO: 1, 2, and 3; respectively;

b) SEQ ID NO: 7, 2, and 3; respectively; and

c) variant of a)-b) comprising 1, 2, or 3 conservative amino acid substitutions; and

wherein said antibody or antigen-binding fragment thereof comprises VL-CDR1, VL-CDR2, and VL-CDR3 sequences selected from the group consisting of:

d) SEQ ID NO: 4, 5, and 6; respectively;

e) SEQ ID NO: 8, 5, and 6; respectively; and

f) variant of d)-e) comprising 1, 2, or 3 conservative amino acid substitutions;

(iii) said antibody comprises a VH sequence derived from SEQ ID NO: 19, wherein said VH sequence comprises a valine (V) or leucine (L) at residue 32 according to Kabat numbering; and wherein said antibody comprises a VL sequence derived from SEQ ID NO: 22, wherein said VL sequence comprises alanine (A) at residue 27E according to Kabat numbering, and a tryptophan (W), and an alanine (A) at residues 50 and 51, respectively, according to Kabat numbering; or

(iv) said antibody comprises VH-CDR1, VH-CDR2, and VH-CDR3 sequences and VL-CDR1, VL-CDR2, and VL-CDR3 sequences selected from the group consisting of:

a) SEQ ID NO: 1, 2, and 3 and SEQ ID NO: 4, 5, and 6, respectively;

b) SEQ ID NO: 7, 2, and 3 and SEQ ID NO: 8, 5, and 6, respectively;

c) SEQ ID NO: 1, 2, and 3 and SEQ ID NO: 8, 5, and 6, respectively; and

d) SEQ ID NO: 7, 2, and 3 and SEQ ID NO: 4, 5, and 6, respectively.

2. The antibody of claim 1(iii), further comprising cysteine-alanine-isoleucine (CAI) in the VH at residues 92-94 according to Kabat numbering.

3. The antibody of any one of claims 1(i) to 1(iii), comprising:

(i) the heavy chain and light chain framework region (FR) sequences derived from human gene IGHV1-69*01 and IGKV4-1*01, respectively, and functional variants thereof;

(ii) heavy chain framework region (VHFR)-1, VHFR-2, VHFR-3, and VHFR-4 sequences set forth in SEQ ID NOS: 29-32, respectively; and light chain framework region (VLFR)-1, VLFR-2, VLFR-3, and VLFR-4 sequences set forth in SEQ ID NOS: 33-36, respectively;

(iii) a VH sequence that is about 90%, about 95%, or about 99% identical to a sequence selected from SEQ ID NOS: 11 and 12, and a VL sequence that is about 90%, about 95%, or about 99% identical to a sequence selected from SEQ ID NOS: 20 and 21; and/or

(iv) a VH sequence selected from SEQ ID NOS: 11 and 12 and a VL sequence selected from SEQ ID NOS: 20 and 21.

4. The antibody of any one of the preceding claims,:

(i) comprising a VH sequence and a VL sequence that are about 90%, about 95%, or about 99% identical to a sequence selected from the group consisting of:

a) SEQ ID NO: 11 and 20, respectively;
b) SEQ ID NO: 12 and 21, respectively;
c) SEQ ID NO: 11 and 21, respectively; and

d) SEQ ID NO: 12 and 20, respectively;

(ii) comprising a VH sequence and a VL sequence selected from the group consisting of:

a) SEQ ID NO: 11 and 20, respectively;
b) SEQ ID NO: 12 and 21, respectively;
c) SEQ ID NO: 11 and 21, respectively; and
d) SEQ ID NO: 12 and 20, respectively;

(iii) comprising a VH sequence of SEQ ID NO: 11 or SEQ ID NO: 12, wherein the VH sequence has Glutamine (Q) instead of Glutamic Acid (E) at residue 1 of SEQ ID NO: 11 or 12;

(iv) comprising a heavy chain constant region sequence selected from the group consisting of SEQ ID NOS: 37-51 or 76 and a light chain constant region sequence selected from SEQ ID NOS: 23 and 24;

(v) comprising a heavy chain constant region sequence set forth in SEQ ID NO: 43 and a light chain constant region sequence set forth in SEQ ID NO: 23;

(vi) wherein the antibody is human, or humanized;

(vii) wherein the antibody is a humanized antibody;

(viii) wherein the antibody has low or no immunogenicity profile;

(ix) wherein the antibody has a humanness score greater than or equal to about 89%;

(x) wherein the antibody has a KD lower than or equal to about 5×10^{-11} molar (M) as measured by SPR at 37°C;

(xi) wherein the antibody or antigen-binding fragment thereof has a KD lower than or equal to about 3×10^{-11} molar (M) as measured by SPR at 37°C;

(xii) which is an antigen-binding fragment;

(xiii) wherein the antibody comprises a Fab, Fab', F(ab')2, Fd, single chain Fv or scFv, disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGACH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb^2, (scFv)2, or scFv-Fc;

(xiv) which is a full length antibody;

(xv) wherein the constant region is an IgG constant region;

(xvi) wherein the constant region is an IgG1 constant region or an IgG4 constant region;

(xvii) wherein the constant region comprises a sequence selected from the group consisting of the human IgG1 sequence set forth in SEQ ID NO: 37, the human IgG1 FAB TAG sequence set forth in SEQ ID NO: 38, the human IgG1 KiH Hole sequence set forth in SEG ID NO: 39, the human IgG1 KiH Knob sequence set forth in SEQ ID NO: 40, the human IgG1 (L235A,G237A) sequence set forth in SEQ ID NO: 41, the human IgG1 YTE sequence set forth in SEQ ID NO: 42, the human IgG1 (L235A, G237A, YTE) sequence set for in SEQ ID NO: 76, the human IgG2DASS sequence set forth in SEQ ID NO: 43, the human IgG4 sequence set forth in SEQ ID NO: 44, the human IgG4 KiH Hole sequence set forth in SEQ ID NO: 45, the human IgG4 KiH Knob sequence set forth in SEQ ID NO: 46, the human IgG4 (L235A,G237A) sequence set forth in SEQ ID NO: 47, the human IgG4 (L235E) sequence set forth in SEQ ID NO: 48, the human IgG4 YTE sequence set forth in SEQ ID NO: 49, the human IgG4 YTE KiH Hole sequence set forth in SEQ ID NO: 50, and the human IgG4 YTE KiH Knob sequence set forth in SEQ ID NO: 51;

(xviii) wherein the heavy chain is an IgG2 heavy chain;

(xix) wherein the heavy chain comprises the IgG2DASS sequence set forth in SEQ ID NO: 43;

(xx) wherein the light chain is a human kappa light chain;

(xxi) wherein the light chain is a human lambda light chain;

(xxii) comprising a full length heavy chain sequence and a full length light chain sequence that is about 90%, about 95%, or about 99% identical to the sequences selected from the group consisting of:

a) SEQ ID NOs: 70 and 71, respectively;
b) SEQ ID Nos: 74 and 71, respectively;
c) SEQ ID NOs: 75 and 71, respectively;
d) SEQ ID NOs: 72 and 73, respectively;
e) SEQ ID NOs: 70 and 73, respectively; and
f) SEQ ID NOs: 72 and 71, respectively;

(xxiii) comprising a full length heavy chain sequence and a full length light chain sequence selected from the group consisting of:

a) SEQ ID NOs: 70 and 71, respectively;

b) SEQ ID Nos: 74 and 71, respectively;

c) SEQ ID NOs: 75 nd 71, respectively;

d) SEQ ID NOs:72 and 73, respectively;

e) SEQ ID NOs: 70 and 73, respectively; and

f) SEQ ID NOs: 72 and 71, respectively;

(xxiv) wherein the heavy chain sequence has Glutamine (Q) instead of Glutamic Acid (E) at residue 1 of SEQ ID NO: 70 72, 74, and 75;

(xxv) wherein the antibody is an antagonist of PACAP; and/or

(xxvi) wherein the antibody specifically binds to PACAP.

5. A nucleic acid encoding the antibody of any one of the preceding claims.

6. A vector comprising the nucleic acid of claim 5.

7. An engineered cell comprising the vector of claim 6.

8. A method of producing an antibody, the method comprising culturing the engineered cell of claim 7 under conditions sufficient for the cell to produce the antibody.

9. A pharmaceutical composition comprising the antibody of any one of claims 1-4 and a pharmaceutically acceptable carrier.

10. Use of the antibody of any one of claims 1-4 or the pharmaceutical composition of claim 9 in the manufacture of a medicament for:
(i) treating or preventing a condition in an individual, wherein the individual is to be administered a therapeutically effective amount of the antibody or the pharmaceutical composition, wherein the condition is selected from the group consisting of: headache (e.g., migraine, cluster headache, refractory migraine), anxiety, depression, PTSD, comorbid conditions (e.g. anxiety/depression/PTSD) with headache (e.g., migraine, cluster headache, refractory migraine), comorbid anxiety disorders with migraine, complex regional pain syndrome, and rosacea;

(ii) treating or preventing migraine in an individual, wherein the individual is to be administered a therapeutically effective amount of the antibody or the pharmaceutical composition;

(iii) treating or preventing migraine in an individual, wherein the individual is to be administered a therapeutically effective amount of the antibody or the pharmaceutical composition, wherein the individual fails to respond to two to four applicable preventive drugs;

(iv) treating or preventing migraine in an individual, wherein the individual is to be administered a therapeutically effective amount of the antibody or the pharmaceutical composition, wherein the individual fails to respond to two to four applicable classes of preventive drugs;

(v) treating or preventing migraine in an individual, wherein the individual fails to respond to two to four applicable preventive drugs or classes of preventive drugs; and the individual is to be administered a therapeutically effective amount of the antibody or the pharmaceutical composition; or

(vi) treating or preventing migraine in an individual who fails to respond to CGRP pathway monoclonal antibodies, wherein the individual is to be administered a therapeutically effective amount of the antibody or the pharmaceutical composition.

11. The use of claim 10(i), wherein the headache is selected from the group consisting of: migraine with aura, migraine without aura, hemiplegic migraine, cluster headache, migrainous neuralgia, chronic headache, episodic migraine, chronic migraine, medication overuse headache, and tension headache.

12. The use of claim 10(iii), wherein the individual fails to respond to two to four applicable preventive drugs selected from the group consisting of: divalproex, sodium valproate, valproate, valproic acid, topiramate, gabapentin, propranolol, timolol, atenolol, metoprolol, nadolol, bisopropol, flunarizine, amitriptyline, nortriptyline, doxepin, fluoxetine and candesartan.

13. The use of claim 10(iv), wherein:

(i) the classes of preventative drugs are selected from the group consisting of: antiepileptics, beta-blockers, tricyclic antidepressants, calcium channel blockers, angiotensin II receptor antagonist, botulinum toxin and CGRP pathway monoclonal antibodies; or

(ii) the classes of preventive drugs are selected from a different cluster, wherein the clusters are defined as follows:

Cluster A: antiepileptics

Cluster B: beta-blockers

Cluster C: tricyclic antidepressants

Cluster D: calcium channel blockers

Cluster E: angiotensin II receptor antagonists

Cluster F, botulinum toxin,

And Cluster G: calcitonin gene related peptide (CGRP) pathway monoclonal antibodies.

14. The use according to claims 10(iii), 10(iv), 12 or 13, wherein the individual fails to respond to two to three, at least two, at least three, at least four, more than two, or more than three preventive drugs or classes of preventive drugs.

15. The use of claim 10(vi), wherein:

(i) the CGRP pathway monoclonal antibodies comprises an anti-CGRP antibody, an anti-CGRP-R antibody, or both;

(ii) the anti-CGRP antibody is selected from fremanezumab, galcanezumab, eptinezumab, or combinations thereof; or

(iii) the anti-CGRP-R antibody is erenumab.