

patients (Schytz *et al.*, Brain, Vol. 132:16-25, 2009; Amin *et al.*, Brain, Vol. 137: 779-794, 2014; Guo *et al.*, Cephalalgia, Vol. 37:125-135, 2017). However, in the same model, VIP does not cause migraine-like headaches in migraine patients (Rahmann *et al.*, Cephalalgia, Vol. 28:226-236, 2008). The lack of migraine-like headache induction from VIP infusion suggests that PACAP38 peptide's effects are mediated through the PAC1 receptor, rather than VPAC1 or VPAC2 receptors, because VIP has a much higher affinity at the latter two receptors. This notion is further supported by animal studies in which PAC1 receptor antagonists inhibit nociceptive neuronal activity in the trigeminocervical complex in an *in vivo* model of migraine (Akerman *et al.*, Sci. Transl. Med., Vol. 7: 308ra157, 2015; Hoffmann *et al.*, Cephalalgia, Vol. 37 (1S): 3, Abstract OC-BA-004, 2017). Taken together, these data suggest that pharmacological agents that inhibit PACAP-activation of the PAC1 receptor have the potential to treat migraine.

SUMMARY

[0008] The present disclosure is based, in part, on the design and generation of high affinity antibodies that specifically bind to and potently inhibit human PAC1. The antibodies of the disclosure have enhanced inhibitory potency against human PAC1 as compared to previously described anti-PAC1 antibodies, with IC50 values in the picomolar range. The isolated antibodies and antigen-binding fragments thereof can be used to inhibit, interfere with, or modulate the biological activity of human PAC1, including inhibiting or reducing PACAP-induced activation of PAC1, inhibiting or reducing vasodilation, and ameliorating or treating symptoms of migraine and other vascular headaches.

[0008a] In one aspect, the present disclosure refers to an isolated antibody or antigen-binding fragment thereof that specifically binds to human pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1), wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein: (a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 108, and 171, respectively; (b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 116, and 171, respectively; (c)

CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively; (d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 92, 145, and 174, respectively; (e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 108, and 172, respectively; (f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 128, and 172, respectively; (g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively; (h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 153, and 171, respectively; (i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 154, and 171, respectively; or (j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 13, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 155, and 171, respectively.

[0008b] In another aspect, the present disclosure refers to an isolated antibody or antigen-binding fragment thereof that specifically binds to human PAC1, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein CDRL1 comprises a sequence selected from SEQ ID NOs: 17-25; CDRL2 comprises a sequence selected from SEQ ID NOs: 27-35; CDRL3 comprises a sequence selected from SEQ ID NOs: 39-51; CDRH1 comprises a sequence selected from SEQ ID NOs: 97-105; CDRH2 comprises a sequence selected from SEQ ID NOs: 167-170; and CDRH3 comprises a sequence selected from SEQ ID NOs: 178-190.

[0008c] In another aspect, the present disclosure refers to an isolated antibody that specifically binds to human PAC1, wherein the antibody comprises a light chain and a heavy chain, wherein: (a) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises

the sequence of SEQ ID NO: 521; (b) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 522; (c) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 523; (d) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 524; (e) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 525; (f) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 526; (g) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 523; (h) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 527; (i) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 528; (j) the light chain comprises the sequence of SEQ ID NO: 508 and the heavy chain comprises the sequence of SEQ ID NO: 529; (k) the light chain comprises the sequence of SEQ ID NO: 510 and the heavy chain comprises the sequence of SEQ ID NO: 531; (l) the light chain comprises the sequence of SEQ ID NO: 511 and the heavy chain comprises the sequence of SEQ ID NO: 532; (m) the light chain comprises the sequence of SEQ ID NO: 512 and the heavy chain comprises the sequence of SEQ ID NO: 533; (n) the light chain comprises the sequence of SEQ ID NO: 513 and the heavy chain comprises the sequence of SEQ ID NO: 534; (o) the light chain comprises the sequence of SEQ ID NO: 514 and the heavy chain comprises the sequence of SEQ ID NO: 535; (p) the light chain comprises the sequence of SEQ ID NO: 515 and the heavy chain comprises the sequence of SEQ ID NO: 535; (q) the light chain comprises the sequence of SEQ ID NO: 516 and the heavy chain comprises the sequence of SEQ ID NO: 532; (r) the light chain comprises the sequence of SEQ ID NO: 517 and the heavy chain comprises the sequence of SEQ ID NO: 536; (s) the light chain comprises the sequence of SEQ ID NO: 509 and the heavy chain comprises the sequence of SEQ ID NO: 532; or (t) the light chain comprises the sequence of SEQ ID NO: 518 and the heavy chain comprises the sequence of SEQ ID NO: 530.

[0008d] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof as described herein and a pharmaceutically acceptable excipient.

[0008e] In another aspect, the present disclosure refers to an isolated polynucleotide that encodes the isolated antibody or antigen-binding fragment thereof as described herein.

[0008f] In yet another aspect, the present disclosure refers to an expression vector comprising the polynucleotide as described herein.

[0008g] In yet another aspect, the present disclosure refers to a host cell comprising the expression vector as described herein.

[0008h] In still another aspect, the present disclosure refers to a method of producing an antibody or antigen-binding fragment thereof that specifically binds to human PAC1 comprising culturing the host cell as described herein under conditions that allow expression of the antibody or antigen-binding fragment thereof; and recovering the antibody or antigen-binding fragment thereof from the culture medium or host cell.

[0008i] In still another aspect, the present disclosure refers to use of the antibody or antigen-binding fragment thereof as described herein for the preparation of a medicament for treating or preventing a headache condition in a patient in need thereof.

[0008j] In still another aspect, the present disclosure refers to use of the antibody or antigen-binding fragment thereof as described herein for the preparation of a medicament for use in combination therapy for treating or preventing a headache condition in a patient in need thereof, wherein said medicament is to be administered to the patient in combination with a second headache therapeutic agent.

[0009] In some examples, the isolated antibodies and antigen-binding fragments thereof specifically bind to human PAC1 at an epitope that comprises one or more amino acids selected from Asp59, Asn60, Ile61, Arg116, Asn117, Thr119, Glu120, Asp121, Gly122, Trp123, Ser124, Glu125, Pro126, Phe127, Pro128, His129, Tyr130, Phe131, Asp132, and Gly135 of SEQ ID NO: 1. In certain examples, the epitope comprises at least amino acids Asn60, Ile61, Glu120, and Asp121 of human PAC1. In these and other examples, the antibodies and antigen-binding fragments of the disclosure comprise specific amino acids at particular positions within the light chain and heavy chain variable regions that interact with these epitope residues. For instance, in one example, the antibodies or antigen-binding fragments comprise a light chain variable region in which the amino acid at position 29 according to AHO numbering is a basic amino acid (e.g. arginine or lysine) that interacts with amino acids Glu120 or Asp121 of human PAC1. In another example, the antibodies or antigen-binding fragments comprise a heavy chain variable region in which the amino acid at position 61 according to AHO numbering is a hydrophobic, basic, or neutral hydrophilic amino acid (e.g. isoleucine, valine, leucine, glutamine, asparagine, arginine,

or lysine) that interacts with amino acids Asn60 or Ile61 of human PAC1. In yet another example, the antibodies or antigen-binding fragments comprise a heavy chain variable region in which the amino acid at position 66 according to AHo numbering is a basic or neutral hydrophilic amino acid (e.g. glutamine, asparagine, arginine, or lysine) that interacts with amino acids Asn60 or Ile61 of human PAC1.

[0010] The anti-PAC1 antibodies and antigen-binding fragments of the disclosure can inhibit ligand-induced activation of the PAC1 receptor. For instance, in some examples, the anti-PAC1 antibodies and antigen-binding fragments inhibit PACAP-induced activation of human PAC1 with an IC₅₀ less than 500 pM as measured by a cell-based cAMP assay. In other examples, the anti-PAC1 antibodies and antigen-binding fragments inhibit PACAP-induced activation of human PAC1 with an IC₅₀ less than 300 pM as measured by a cell-based cAMP assay. In certain examples, the anti-PAC1 antibodies and antigen-binding fragments inhibit PACAP-induced activation of the human PAC1 receptor with an IC₅₀ between about 50 pM and about 500 pM as measured by a cell-based cAMP assay.

[0011] In some examples, the anti-PAC1 antibodies and antigen binding fragments of the disclosure cross-react with PAC1 receptors from other species. In one example, the anti-PAC1 antibodies or antigen-binding fragments specifically bind to and inhibit PACAP-induced activation of the cynomolgus monkey PAC1 receptor. In such an example, the anti-PAC1 antibodies or antigen-binding fragments may inhibit PACAP-induced activation of the cynomolgus monkey PAC1 receptor with an IC₅₀ between about 0.1 nM and about 1 nM or between about 50 pM and about 500 pM as measured by a cell-based cAMP assay. In another example, the anti-PAC1 antibodies or antigen-binding fragments specifically bind to and inhibit PACAP-induced activation of the rat PAC1 receptor. The anti-PAC1 antibodies or antigen-binding fragments may inhibit PACAP-induced activation of the rat PAC1 receptor with an IC₅₀ less than 10 nM, for example with an IC₅₀ between about 0.1 nM and about 10 nM or between about 100 pM and about 2 nM as measured by a cell-based cAMP assay.

[0012] In certain examples, the anti-PAC1 antibodies or antigen-binding fragments of the disclosure comprise a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3. The light chain and heavy chain variable regions or CDRs may be from any of the anti-PAC1 antibodies described herein.

For instance, in some examples, the anti-PAC1 antibodies or antigen-binding fragments comprise a CDRL1 comprising a sequence selected from SEQ ID NOs: 5-16; a CDRL2 comprising the sequence of SEQ ID NO: 26; a CDRL3 comprising a sequence selected from SEQ ID NOs: 36-38; a CDRH1 comprising a sequence selected from SEQ ID NOs: 88-96; a CDRH2 comprising a sequence selected from SEQ ID NOs: 106-166; and a CDRH3 comprising a sequence selected from SEQ ID NOs: 171-177. In other examples, the anti-PAC1 antibodies or antigen-binding fragments comprise a CDRL1 comprising a sequence selected from SEQ ID NOs: 17-25; a CDRL2 comprising a sequence selected from SEQ ID NOs: 27-35; a CDRL3 comprising a sequence selected from SEQ ID NOs: 39-51; a CDRH1 comprising a sequence selected from SEQ ID NOs: 97-105; a CDRH2 comprising a sequence selected from SEQ ID NOs: 167-170; and a CDRH3 comprising a sequence selected from SEQ ID NOs: 178-190.

[0013] In some examples, the anti-PAC1 antibodies or antigen-binding fragments of the disclosure comprise a light chain variable region that comprises a sequence that is at least 90% identical or at least 95% identical to a sequence selected from SEQ ID NOs: 54-66 and SEQ ID NOs: 68-87. In these and other examples, the anti-PAC1 antibodies or antigen-binding fragments of the disclosure comprise a heavy chain variable region that comprises a sequence that is at least 90% identical or at least 95% identical to a sequence selected from SEQ ID NOs: 191-312. In one example, the anti-PAC1 antibodies or antigen-binding fragments comprise a light chain variable region comprising a sequence selected from SEQ ID NOs: 54-66 and a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 191-295. In another example, the anti-PAC1 antibodies or antigen-binding fragments comprise a light chain variable region comprising a sequence selected from SEQ ID NOs: 68-87 and a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 296-312.

[0014] In any of the examples described herein, including the examples described above, the anti-PAC1 antibody or antigen-binding fragment of the disclosure is a monoclonal antibody or antigen-binding fragment thereof. In some examples, the monoclonal antibody or antigen-binding fragment thereof is a chimeric antibody or antigen-binding fragment thereof. In other examples, the monoclonal antibody or antigen-binding fragment thereof is a humanized antibody or antigen-binding fragment thereof. In yet other examples, the monoclonal antibody or antigen-binding fragment thereof is a fully human antibody or antigen-binding fragment thereof. The monoclonal antibody can be of any isotype, such as a human IgG1, IgG2, IgG3, or IgG4. In one

particular example, the monoclonal antibody is a human IgG1 antibody. In another particular example, the monoclonal antibody is a human IgG2 antibody. The monoclonal antibody may comprise a light chain that comprises a human kappa constant region. In some examples, the human kappa constant region comprises the sequence of SEQ ID NO: 318 or SEQ ID NO: 319. Thus, the anti-PAC1 antibodies or antigen-binding fragments of the disclosure may comprise a light chain that comprises any of the light chain variable region sequences listed in Table 1A fused to a human kappa constant region comprising the sequence of SEQ ID NO: 318 or SEQ ID NO: 319. In other examples, the monoclonal antibody may comprise a light chain that comprises a human lambda constant region. In certain examples, the human lambda constant region comprises the sequence of SEQ ID NO: 315. Thus, in some examples, the anti-PAC1 antibodies or antigen-binding fragments of the disclosure may comprise a light chain that comprises any of the light chain variable region sequences listed in Table 1A fused to a human lambda constant region comprising the sequence of SEQ ID NO: 315.

[0015] In certain examples, the anti-PAC1 antibodies or antigen-binding fragments of the disclosure may contain one or more modifications that affect the glycosylation of the antibody or antigen-binding fragment. In some examples, the antibody or antigen-binding fragment comprises one or more mutations to reduce or eliminate glycosylation. In such examples, the aglycosylated antibody may comprise a mutation at amino acid position N297 (according to the EU numbering scheme), such as a N297G mutation, in its heavy chain. The aglycosylated antibody may comprise further mutations to stabilize the antibody structure. Such mutations can include pairs of cysteine substitutions, such as A287C and L306C, V259C and L306C, R292C and V302C, and V323C and I332C (amino acid positions according to the EU numbering scheme). In one example, the aglycosylated antibody comprises R292C and V302C mutations (according to the EU numbering scheme) in its heavy chain. In certain examples, the aglycosylated anti-PAC1 antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 324 or SEQ ID NO: 325.

[0016] The present disclosure also includes isolated polynucleotides and expression vectors encoding the anti-PAC1 antibodies and antigen-binding fragments described herein as well as host cells, such as CHO cells, comprising the encoding polynucleotides and expression vectors. In certain examples, the present disclosure includes methods for producing the anti-PAC1 antibodies and antigen-binding fragments described herein. In one example, the method

comprises culturing a host cell comprising an expression vector encoding the anti-PAC1 antibody or antigen-binding fragment under conditions that allow expression of the antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the culture medium or host cell.

[0017] The anti-PAC1 antibodies or antigen-binding fragments described herein can be used in the manufacture of a pharmaceutical composition or medicament for the treatment or prevention of conditions associated with PAC1 biological activity, such as headache, migraine, cluster headache, and vasomotor symptoms. Thus, the present disclosure also provides a pharmaceutical composition comprising an anti-PAC1 antibody or antigen-binding fragment described herein and a pharmaceutically acceptable excipient. The pharmaceutical compositions can be used in any of the methods described herein.

[0018] In certain examples, the present disclosure provides methods for treating or preventing a headache condition in a patient in need thereof comprising administering to the patient an effective amount of an anti-PAC1 antibody or antigen-binding fragment described herein. In some examples, the headache condition to be treated or prevented with the methods of the disclosure is migraine. The migraine can be episodic migraine or chronic migraine. In other examples, the headache condition to be treated or prevented with the methods of the disclosure is cluster headache. In certain examples, the methods provide prophylactic treatment for these conditions.

[0019] In some examples of the methods of the disclosure, the methods comprise administering a second headache therapeutic agent to the patient in combination with an anti-PAC1 antibody or antigen-binding fragment of the disclosure. The second headache therapeutic agent can be an acute headache therapeutic agent, such as a serotonin receptor agonist (e.g. agonist of a 5HT_{1B}, 5HT_{1D}, and/or 5HT_{1F} serotonin receptor). In some examples, the acute headache therapeutic agent is a triptan, ergotamine, non-steroidal anti-inflammatory drug, or an opioid. In other examples, the second headache therapeutic agent to be administered in combination with an anti-PAC1 antibody or antigen-binding fragment of the disclosure is a prophylactic headache therapeutic agent, such as an antiepileptic, a beta-blocker, an anti-depressant, or onabotulinum toxin A. The second headache therapeutic agent may be administered to the patient before, after, or concurrently with an anti-PAC1 antibody or antigen-binding fragment of the disclosure.

[0020] In certain examples of the methods of the disclosure, the methods comprise administering a CGRP pathway antagonist to the patient in combination with an anti-PAC1 antibody or antigen-binding fragment of the disclosure. The CGRP pathway antagonist can be an antagonist of the human CGRP receptor, such as an antibody that specifically binds to the human CGRP receptor. In one example, the CGRP pathway antagonist administered in combination with an anti-PAC1 antibody or antigen-binding fragment of the disclosure is erenumab. In other examples, the CGRP pathway antagonist can be an antagonist of the CGRP ligand, such as an antibody that specifically binds to human α -CGRP and/or β -CGRP. In one such example, the CGRP pathway antagonist administered in combination with an anti-PAC1 antibody or antigen-binding fragment of the disclosure is fremanezumab. In another such example, the CGRP pathway antagonist administered in combination with an anti-PAC1 antibody or antigen-binding fragment of the disclosure is galcanezumab. In yet another such example, the CGRP pathway antagonist administered in combination with an anti-PAC1 antibody or antigen-binding fragment of the disclosure is eptinezumab.

[0021] The present disclosure also includes methods of inhibiting vasodilation in a patient in need thereof. In one example, the method comprises administering to the patient an effective amount of any of the anti-PAC1 antibodies or antigen-binding fragments described herein. In some examples, the patient in need of treatment has a headache condition, such as migraine or cluster headache. In other examples, the patient in need of treatment has vasomotor symptoms (e.g. hot flashes, facial flushing, sweating, and night sweats), such as those associated with menopause.

[0022] The use of the anti-PAC1 antibodies or antigen-binding fragments in any of the methods disclosed herein or for preparation of medicaments for administration according to any of the methods disclosed herein is specifically contemplated. For instance, the present disclosure includes an anti-PAC1 antibody or antigen-binding fragment for use in a method for treating or preventing a headache condition in a patient in need thereof. The headache condition includes migraine (e.g. episodic and chronic migraine) and cluster headache. In some examples, the present disclosure provides an anti-PAC1 antibody or antigen-binding fragment for use in a method for inhibiting vasodilation in a patient in need thereof. In such examples, the patient may be diagnosed with or have a headache condition. In other examples, the present disclosure provides an anti-PAC1 antibody or antigen-binding fragment for use in a method for inhibiting

activation of human PAC1 receptor in a patient having a headache condition. The headache condition may be migraine (e.g. episodic or chronic migraine) or cluster headache.

[0023] The present disclosure also includes the use of an anti-PAC1 antibody or antigen-binding fragment in the preparation of a medicament for treating or preventing a headache condition in a patient in need thereof. The headache condition includes migraine (e.g. episodic and chronic migraine) and cluster headache. In certain examples, the present disclosure encompasses the use of an anti-PAC1 antibody or antigen-binding fragment in the preparation of a medicament for inhibiting vasodilation in a patient in need thereof. In such examples, the patient may be diagnosed with or have a headache condition. In other examples, the present disclosure includes the use of an anti-PAC1 antibody or antigen-binding fragment in the preparation of a medicament for inhibiting activation of human PAC1 receptor in a patient having a headache condition. The headache condition may be migraine (e.g. episodic or chronic migraine) or cluster headache.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1A is a front view of the crystal structure of the complex between human PAC1 extracellular domain (ECD) and the Fab fragment of the 29G4v9 antibody. VL = light chain variable region; CL = light chain constant region; VH = heavy chain variable region; and CH1 = heavy chain CH1 constant region.

[0025] Figure 1B is a side view of the crystal structure of the complex between human PAC1 ECD and the Fab fragment of the 29G4v9 antibody. The view depicts the structure shown in Figure 1A rotated 90° to the left. In this view, the light chain variable region (VL) is positioned behind the heavy chain variable region (VH), and the light chain constant region (CL) is positioned behind the heavy chain CH1 constant region.

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to human pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1), wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein:

(a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 108, and 171, respectively;

(b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 116, and 171, respectively;

(c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively;

(d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 92, 145, and 174, respectively;

(e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 108, and 172, respectively;

(f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 128, and 172, respectively;

(g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 134, and 171, respectively;

(h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 153, and 171, respectively;

(i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 154, and 171, respectively; or

(j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 13, 26, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 88, 155, and 171, respectively.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the light chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 54-66, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 54-66, or (iii) a sequence selected from SEQ ID NOs: 54-66.

3. The isolated antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the heavy chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 191-295, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 191-295, or (iii) a sequence selected from SEQ ID NOs: 191-295.

4. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 3, wherein:

(a) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 194;

(b) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 203;

(c) the light chain variable region comprises the sequence of SEQ ID NO: 55 and the heavy chain variable region comprises the sequence of SEQ ID NO: 228;

(d) the light chain variable region comprises the sequence of SEQ ID NO: 55 and the heavy chain variable region comprises the sequence of SEQ ID NO: 274;

(e) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 214;

(f) the light chain variable region comprises the sequence of SEQ ID NO: 55 and the heavy chain variable region comprises the sequence of SEQ ID NO: 240;

(g) the light chain variable region comprises the sequence of SEQ ID NO: 54 and the heavy chain variable region comprises the sequence of SEQ ID NO: 228;

(h) the light chain variable region comprises the sequence of SEQ ID NO: 62 and the heavy chain variable region comprises the sequence of SEQ ID NO: 282;

(i) the light chain variable region comprises the sequence of SEQ ID NO: 62 and the heavy chain variable region comprises the sequence of SEQ ID NO: 283; or

(j) the light chain variable region comprises the sequence of SEQ ID NO: 63 and the heavy chain variable region comprises the sequence of SEQ ID NO: 284.

5. An isolated antibody or antigen-binding fragment thereof that specifically binds to human PAC1, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein CDRL1 comprises a sequence selected from SEQ ID NOs: 17-25; CDRL2 comprises a sequence selected from SEQ ID NOs: 27-35; CDRL3 comprises a sequence selected from SEQ ID NOs: 39-51; CDRH1 comprises a sequence selected from SEQ ID NOs: 97-105; CDRH2 comprises a sequence selected from SEQ ID NOs: 167-170; and CDRH3 comprises a sequence selected from SEQ ID NOs: 178-190.

6. The isolated antibody or antigen-binding fragment thereof of claim 5, wherein:

(a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 25, 31, and 42, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 190, respectively;

(b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 20, 30, and 44, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 100, 168, and 182, respectively;

(c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 33, and 42, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 99, 168, and 187, respectively;

(d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 23, 31, and 50, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 97, 167, and 178, respectively;

(e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 31, and 44, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 189, respectively;

(f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 27, and 39, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 100, 168, and 182, respectively;

(g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 18, 31, and 46, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 179, respectively;

(h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 28, and 40, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 98, 168, and 179, respectively;

(i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 18, 30, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 100, 168, and 182, respectively; or

(j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 22, 28, and 49, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 102, 169, and 182, respectively.

7. The isolated antibody or antigen-binding fragment thereof of claim 5 or 6, wherein the light chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 68-87, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 68-87, or (iii) a sequence selected from SEQ ID NOs: 68-87.

8. The isolated antibody or antigen-binding fragment thereof of any one of claims 5 to 7, wherein the heavy chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 296-312, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 296-312, or (iii) a sequence selected from SEQ ID NOs: 296-312.

9. The isolated antibody or antigen-binding fragment thereof of any one of claims 5 to 8, wherein:

(a) the light chain variable region comprises the sequence of SEQ ID NO: 85 and the heavy chain variable region comprises the sequence of SEQ ID NO: 312;

(b) the light chain variable region comprises the sequence of SEQ ID NO: 72 and the heavy chain variable region comprises the sequence of SEQ ID NO: 300;

(c) the light chain variable region comprises the sequence of SEQ ID NO: 81 and the heavy chain variable region comprises the sequence of SEQ ID NO: 307;

(d) the light chain variable region comprises the sequence of SEQ ID NO: 78 and the heavy chain variable region comprises the sequence of SEQ ID NO: 296;

(e) the light chain variable region comprises the sequence of SEQ ID NO: 83 and the heavy chain variable region comprises the sequence of SEQ ID NO: 310;

(f) the light chain variable region comprises the sequence of SEQ ID NO: 87 and the heavy chain variable region comprises the sequence of SEQ ID NO: 300;

(g) the light chain variable region comprises the sequence of SEQ ID NO: 74 and the heavy chain variable region comprises the sequence of SEQ ID NO: 297;

(h) the light chain variable region comprises the sequence of SEQ ID NO: 68 and the heavy chain variable region comprises the sequence of SEQ ID NO: 297;

(i) the light chain variable region comprises the sequence of SEQ ID NO: 71 and the heavy chain variable region comprises the sequence of SEQ ID NO: 300; or

(j) the light chain variable region comprises the sequence of SEQ ID NO: 77 and the heavy chain variable region comprises the sequence of SEQ ID NO: 304.

10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof is a monoclonal antibody or antigen-binding fragment thereof.

11. The isolated antibody or antigen-binding fragment thereof of claim 10, wherein the monoclonal antibody or antigen-binding fragment thereof is a humanized antibody or antigen-binding fragment thereof or a fully human antibody or antigen-binding fragment thereof.

12. The isolated antibody or antigen-binding fragment thereof of claim 10 or 11, wherein the monoclonal antibody comprises a light chain that comprises a human kappa constant region.

13. The isolated antibody or antigen-binding fragment thereof of claim 12, wherein the human kappa constant region comprises the sequence of SEQ ID NO: 318 or SEQ ID NO: 319.

14. The isolated antibody or antigen-binding fragment thereof of claim 10 or 11, wherein the monoclonal antibody comprises a light chain that comprises a human lambda constant region.

15. The isolated antibody or antigen-binding fragment thereof of claim 14, wherein the human lambda constant region comprises the sequence of SEQ ID NO: 315.

16. The isolated antibody or antigen-binding fragment thereof of any one of claims 10 to 15, wherein the monoclonal antibody is a human IgG1, IgG2, IgG3, or IgG4 antibody.

17. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the monoclonal antibody is a human IgG1 antibody.
18. The isolated antibody or antigen-binding fragment thereof of claim 17, wherein the monoclonal antibody is an aglycosylated human IgG1 antibody.
19. The isolated antibody or antigen-binding fragment thereof of claim 18, wherein the monoclonal antibody comprises a mutation at amino acid position N297 according to EU numbering in its heavy chain.
20. The isolated antibody or antigen-binding fragment thereof of claim 19, wherein the mutation is N297G.
21. The isolated antibody or antigen-binding fragment thereof of claim 19 or 20, wherein the monoclonal antibody further comprises R292C and V302C mutations according to EU numbering in its heavy chain.
22. The isolated antibody or antigen-binding fragment thereof of claim 18, wherein the monoclonal antibody comprises a heavy chain constant region that comprises the sequence of SEQ ID NO: 324 or SEQ ID NO: 325.
23. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 22, wherein the antibody or antigen-binding fragment thereof inhibits PACAP-induced activation of rat PAC1 with an IC50 less than 10 nM as measured by a cell-based cAMP assay.
24. An isolated antibody that specifically binds to human PAC1, wherein the antibody comprises a light chain and a heavy chain, wherein:
 - (a) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 521;

(b) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 522;

(c) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 523;

(d) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 524;

(e) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 525;

(f) the light chain comprises the sequence of SEQ ID NO: 504 and the heavy chain comprises the sequence of SEQ ID NO: 526;

(g) the light chain comprises the sequence of SEQ ID NO: 506 and the heavy chain comprises the sequence of SEQ ID NO: 523;

(h) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 527;

(i) the light chain comprises the sequence of SEQ ID NO: 507 and the heavy chain comprises the sequence of SEQ ID NO: 528;

(j) the light chain comprises the sequence of SEQ ID NO: 508 and the heavy chain comprises the sequence of SEQ ID NO: 529;

(k) the light chain comprises the sequence of SEQ ID NO: 510 and the heavy chain comprises the sequence of SEQ ID NO: 531;

(l) the light chain comprises the sequence of SEQ ID NO: 511 and the heavy chain comprises the sequence of SEQ ID NO: 532;

(m) the light chain comprises the sequence of SEQ ID NO: 512 and the heavy chain comprises the sequence of SEQ ID NO: 533;

(n) the light chain comprises the sequence of SEQ ID NO: 513 and the heavy chain comprises the sequence of SEQ ID NO: 534;

(o) the light chain comprises the sequence of SEQ ID NO: 514 and the heavy chain comprises the sequence of SEQ ID NO: 535;

(p) the light chain comprises the sequence of SEQ ID NO: 515 and the heavy chain comprises the sequence of SEQ ID NO: 535;

(q) the light chain comprises the sequence of SEQ ID NO: 516 and the heavy chain comprises the sequence of SEQ ID NO: 532;

(r) the light chain comprises the sequence of SEQ ID NO: 517 and the heavy chain comprises the sequence of SEQ ID NO: 536;

(s) the light chain comprises the sequence of SEQ ID NO: 509 and the heavy chain comprises the sequence of SEQ ID NO: 532; or

(t) the light chain comprises the sequence of SEQ ID NO: 518 and the heavy chain comprises the sequence of SEQ ID NO: 530.

25. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 24 and a pharmaceutically acceptable excipient.

26. An isolated polynucleotide that encodes the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 24.

27. An expression vector comprising the polynucleotide of claim 26.

28. A host cell comprising the expression vector of claim 27.

29. A method of producing an antibody or antigen-binding fragment thereof that specifically binds to human PAC1 comprising culturing the host cell of claim 28 under conditions that allow expression of the antibody or antigen-binding fragment thereof; and recovering the antibody or antigen-binding fragment thereof from the culture medium or host cell.

30. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 24 for the preparation of a medicament for treating or preventing a headache condition in a patient in need thereof.

31. The use of claim 30, wherein the headache condition is migraine.
32. The use of claim 31, wherein the migraine is episodic migraine.
33. The use of claim 31, wherein the migraine is chronic migraine.
34. The use of claim 30, wherein the headache condition is cluster headache.
35. The use of any one of claims 30 to 34, wherein the treatment is a prophylactic treatment.
36. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 24 for the preparation of a medicament for use in combination therapy for treating or preventing a headache condition in a patient in need thereof, wherein said medicament is to be administered to the patient in combination with a second headache therapeutic agent.
37. The use of claim 36, wherein the headache condition is as defined in any one of claims 31 to 34.
38. The use of claim 36 or 37, wherein the second headache therapeutic agent is an acute headache therapeutic agent.
39. The use of claim 38, wherein the acute headache therapeutic agent is a 5HT_{1B}, 5HT_{1D} and/or 5HT_{1F} serotonin receptor agonist.
40. The use of claim 39, wherein the serotonin receptor agonist is a triptan or ergotamine.
41. The use of claim 38, wherein the acute headache therapeutic agent is a non-steroidal anti-inflammatory drug or an opioid.

42. The use of claim 36 or 37, wherein the second headache therapeutic agent is a prophylactic headache therapeutic agent.
43. The use of claim 42, wherein the prophylactic headache therapeutic agent is an antiepileptic, a beta-blocker, an anti-depressant, onabotulinum toxin A, or a CGRP pathway antagonist.
44. The use of claim 43, wherein the CGRP pathway antagonist is a human CGRP receptor antagonist.
45. The use of claim 44, wherein the human CGRP receptor antagonist is a monoclonal antibody that specifically binds to the human CGRP receptor.
46. The use of claim 45, wherein the anti-CGRP receptor monoclonal antibody is erenumab.