

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.

[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.

[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.

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. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 4, wherein the antibody or antigen-binding fragment thereof is a monoclonal antibody or antigen-binding fragment thereof.

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

7. The isolated antibody or antigen-binding fragment thereof of claim 5 or 6, wherein the monoclonal antibody comprises a light chain that comprises a human kappa constant region.

8. The isolated antibody or antigen-binding fragment thereof of claim 7, wherein the human kappa constant region comprises the sequence of SEQ ID NO: 318 or SEQ ID NO: 319.

9. The isolated antibody or antigen-binding fragment thereof of claim 5 or 6, wherein the monoclonal antibody comprises a light chain that comprises a human lambda constant region.

10. The isolated antibody or antigen-binding fragment thereof of claim 9, wherein the human lambda constant region comprises the sequence of SEQ ID NO: 315.
11. The isolated antibody or antigen-binding fragment thereof of any one of claims 5 to 10, wherein the monoclonal antibody is a human IgG1, IgG2, IgG3, or IgG4 antibody.
12. The isolated antibody or antigen-binding fragment thereof of claim 11, wherein the monoclonal antibody is a human IgG1 antibody.
13. The isolated antibody or antigen-binding fragment thereof of claim 12, wherein the monoclonal antibody is an aglycosylated human IgG1 antibody.
14. The isolated antibody or antigen-binding fragment thereof of claim 13, wherein the monoclonal antibody comprises a mutation at amino acid position N297 according to EU numbering in its heavy chain.
15. The isolated antibody or antigen-binding fragment thereof of claim 14, wherein the mutation is N297G.
16. The isolated antibody or antigen-binding fragment thereof of claim 14 or 15, wherein the monoclonal antibody further comprises R292C and V302C mutations according to EU numbering in its heavy chain.
17. The isolated antibody or antigen-binding fragment thereof of claim 13, wherein the monoclonal antibody comprises a heavy chain constant region that comprises the sequence of SEQ ID NO: 324 or SEQ ID NO: 325.

18. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 17, 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.

19. 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; or

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

20. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 19 and a pharmaceutically acceptable excipient.

21. An isolated polynucleotide that encodes the isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 19.
22. An expression vector comprising the polynucleotide of claim 21.
23. A host cell comprising the expression vector of claim 22.
24. A method of producing an antibody or antigen-binding fragment thereof that specifically binds to human PAC1 comprising culturing the host cell of claim 23 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.
25. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 19 for the preparation of a medicament for treating or preventing a headache condition in a patient in need thereof.
26. The use of claim 25, wherein the headache condition is migraine.
27. The use of claim 26, wherein the migraine is episodic migraine.
28. The use of claim 26, wherein the migraine is chronic migraine.
29. The use of claim 25, wherein the headache condition is cluster headache.
30. The use of any one of claims 25 to 29, wherein the treatment is a prophylactic treatment.
31. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 19 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.

32. The use of claim 31, wherein the headache condition is as defined in any one of claims 26 to 29.

33. The use of claim 31 or 32, wherein the second headache therapeutic agent is an acute headache therapeutic agent.

34. The use of claim 33, wherein the acute headache therapeutic agent is a 5HT1B, 5HT1D and/or 5HT1F serotonin receptor agonist.

35. The use of claim 34, wherein the serotonin receptor agonist is a triptan or ergotamine.

36. The use of claim 33, wherein the acute headache therapeutic agent is a non-steroidal anti-inflammatory drug or an opioid.

37. The use of claim 31 or 32, wherein the second headache therapeutic agent is a prophylactic headache therapeutic agent.

38. The use of claim 37, wherein the prophylactic headache therapeutic agent is an antiepileptic, a beta-blocker, an anti-depressant, onabotulinum toxin A, or a CGRP pathway antagonist.

39. The use of claim 38, wherein the CGRP pathway antagonist is a human CGRP receptor antagonist.

40. The use of claim 39, wherein the human CGRP receptor antagonist is a monoclonal antibody that specifically binds to the human CGRP receptor.

41. The use of claim 40, wherein the anti-CGRP receptor monoclonal antibody is erenumab.