PACAP38 and PACAP27 has not been shown to be different from each other. Unless indicated otherwise herein, PACAP or PACAP38 will be used to represent PACAP38, and PACAP27 will be used to specify PACAP27.

Three PACAP receptors have been reported: one that binds PACAP with high affinity and has a much lower affinity for VIP (PAC1 receptor, or simply "PAC1"), and two that recognize PACAP and VIP essentially equally well (VPAC1 and VPAC2 receptors, or simply "VPAC1" or "VPAC2", respectively) (Vaudry, D., et al. "Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery.", Pharmacol Rev. 2009; Sep 61(3):283-357).

PACAP is capable of binding all three receptors (PAC1, VPAC1, VPAC2) with similar potency and is thus not particularly selective. VIP, on the other hand, binds with significantly higher affinity to VPAC1 and VPAC2, as compared with PAC1. Maxadilan, a 65 amino acid peptide originally isolated from the sand-fly (Lerner, E.A., et al., "Isolation of maxadilan, a potent vasodilatory peptide from the salivary glands of the sand fly Lutzomyia longipalpis", J Biol Chem. 1991 Jun 15; 266(17):11234-6; Lerner, E.A., et al., "Maxadilan, a PAC1 receptor agonist from sand flies", Peptides. Sep 2007; 28(9): 1651–1654.), is exquisitely selective for PAC1 compared with VPAC1 or VPAC2, and can thus be used as a PAC1-selective agonist.

SUMMARY

In one aspect, the present invention refers to an isolated antibody or antigen-binding fragment thereof that specifically binds human pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1), comprising (A) a light chain CDR1 (CDRL1) comprising the sequence of SEQ ID NO: 196 or SEQ ID NO: 197; (B) a light chain CDR2 (CDRL2) comprising the sequence of SEQ ID NO: 209; (C) a light chain CDR3 (CDRL3) comprising the sequence of SEQ ID NO: 215; (D) a heavy chain CDR1 (CDRH1) comprising the sequence of SEQ ID NO: 223; (E) a heavy chain CDR2 (CDRH2) comprising the sequence of SEQ ID NO: 237; and (F) a heavy chain CDR3 (CDRH3) comprising the sequence of SEQ ID NO: 247. In another aspect, the present invention refers to an isolated polynucleotide that encodes an antibody or antigen-binding fragment thereof of the present invention. In still another aspect, the present invention refers to an expression vector comprising the polynucleotide of the present invention. In still another aspect, the present invention refers to a cell line transformed with the expression vector of the present invention. In another aspect the present invention refers to a method of making an antibody or antigen-binding fragment thereof of the present invention, comprising preparing the antibody or antigen-binding fragment thereof

from the cell line of the present invention that secretes the antibody or antigen-binding fragment thereof. In another aspect, the present invention refers to a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of the present invention and a pharmaceutically acceptable excipient. In still another aspect, the present invention refers to the use of the antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for treating headache in a patient. In one example, the disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising: (A) a light chain CDR1 comprising (i) an amino acid sequence selected from the group consisting of the LC CDR1 sequences set forth in Table 4A, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the LC CDR1 sequences set forth in Table 4A, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the LC CDR1 sequences set forth in Table 4A; (B) a light chain CDR2 comprising (i) an amino acid sequence selected from the group consisting of the LC CDR2 sequences set forth in Table 4A, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the LC CDR2 sequences set forth in Table 4A, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the LC CDR2 sequences set forth in Table 4A; and (C) a light chain CDR3 comprising (i) an amino acid sequence selected from the group consisting of the LC CDR3 sequences set forth in Table 4A, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the LC CDR3 sequences set forth in Table

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof that specifically binds human pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1), comprising

(A) a light chain CDR1 (CDRL1) comprising the sequence of SEQ ID NO: 196 or SEQ ID NO: 197;

(B) a light chain CDR2 (CDRL2) comprising the sequence of SEQ ID NO: 209;

(C) a light chain CDR3 (CDRL3) comprising the sequence of SEQ ID NO: 215;

(D) a heavy chain CDR1 (CDRH1) comprising the sequence of SEQ ID NO: 223;

(E) a heavy chain CDR2 (CDRH2) comprising the sequence of SEQ ID NO: 237; and

(F) a heavy chain CDR3 (CDRH3) comprising the sequence of SEQ ID NO: 247.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein

CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NO: 223, SEQ ID NO: 237, and SEQ ID NO: 247, respectively, and CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NO: 197, SEQ ID NO: 209, and SEQ ID NO: 215, respectively.

3. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NO: 223, SEQ ID NO: 237, and SEQ ID NO: 247, respectively and CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NO: 196, SEQ ID NO: 209, and SEQ ID NO: 215, respectively.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising a light chain variable region and a heavy chain variable region, wherein the light chain variable region comprises a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 152-159 and the heavy chain variable region comprises a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 172-182.

5. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising a light chain variable region and a heavy chain variable region, wherein:

(a) the light chain variable region comprises the sequence of SEQ ID NO: 152 and the heavy chain variable region comprises the sequence of SEQ ID NO: 172;

(b) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 172;

(c) the light chain variable region comprises the sequence of SEQ ID NO: 154 and the heavy chain variable region comprises the sequence of SEQ ID NO: 172;

(d) the light chain variable region comprises the sequence of SEQ ID NO: 152 and the heavy chain variable region comprises the sequence of SEQ ID NO: 173;

(e) the light chain variable region comprises the sequence of SEQ ID NO: 152 and the heavy chain variable region comprises the sequence of SEQ ID NO: 174;

(f) the light chain variable region comprises the sequence of SEQ ID NO: 155 and the heavy chain variable region comprises the sequence of SEQ ID NO: 173;

(g) the light chain variable region comprises the sequence of SEQ ID NO: 155 and the heavy chain variable region comprises the sequence of SEQ ID NO: 174;

(h) the light chain variable region comprises the sequence of SEQ ID NO: 155 and the heavy chain variable region comprises the sequence of SEQ ID NO: 172;

(i) the light chain variable region comprises the sequence of SEQ ID NO: 152 and the heavy chain variable region comprises the sequence of SEQ ID NO: 175;

(j) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 174;

(k) the light chain variable region comprises the sequence of SEQ ID NO: 156 and the heavy chain variable region comprises the sequence of SEQ ID NO: 174;

(l) the light chain variable region comprises the sequence of SEQ ID NO: 157 and the heavy chain variable region comprises the sequence of SEQ ID NO: 174;

(m) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 176;

(n) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 177;

(o) the light chain variable region comprises the sequence of SEQ ID NO: 157 and the heavy chain variable region comprises the sequence of SEQ ID NO: 176;

(p) the light chain variable region comprises the sequence of SEQ ID NO: 157 and the heavy chain variable region comprises the sequence of SEQ ID NO: 177;

(q) the light chain variable region comprises the sequence of SEQ ID NO: 157 and the heavy chain variable region comprises the sequence of SEQ ID NO: 178;

(r) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 178;

(s) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 179;

(t) the light chain variable region comprises the sequence of SEQ ID NO: 156 and the heavy chain variable region comprises the sequence of SEQ ID NO: 179;

(u) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 180;

(v) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 181;

(w) the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 182; or

(x) the light chain variable region comprises the sequence of SEQ ID NO: 156 and the heavy chain variable region comprises the sequence of SEQ ID NO: 182.

6. The isolated antibody or antigen-binding fragment thereof of claim 5, wherein the light chain variable region comprises the sequence of SEQ ID NO: 153 and the heavy chain variable region comprises the sequence of SEQ ID NO: 182.

7. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody comprises:

(a) a light chain comprising the sequence of SEQ ID NO: 78 and a heavy chain comprising a sequence selected from SEQ ID NOs: 101-112;

(b) a light chain comprising the sequence of SEQ ID NO: 79 and a heavy chain comprising a sequence selected from SEQ ID NOs: 101-103, 107-109, and 113-133;

(c) a light chain comprising the sequence of SEQ ID NO: 80 and a heavy chain comprising a sequence selected from SEQ ID NOs: 101-103;

(d) a light chain comprising the sequence of SEQ ID NO: 81 and a heavy chain comprising a sequence selected from SEQ ID NOs: 101-109;

(e) a light chain comprising the sequence of SEQ ID NO: 82 and a heavy chain comprising a sequence selected from SEQ ID NOs: 107-109, 122-124, and 131-133; or

(f) a light chain comprising the sequence of SEQ ID NO: 83 and a heavy chain comprising a sequence selected from SEQ ID NOs: 107-109 and 113-121.

8. The isolated antibody or antigen-binding fragment thereof of claim 7, wherein the antibody comprises a light chain comprising the sequence of SEQ ID NO: 79 and a heavy chain comprising the sequence of SEQ ID NO: 131.

9. The isolated antibody or antigen-binding fragment thereof of claim 7, wherein the antibody comprises a light chain comprising the sequence of SEQ ID NO: 79 and a heavy chain comprising the sequence of SEQ ID NO: 132.

10. The isolated antibody or antigen-binding fragment thereof of claim 7, wherein the antibody comprises a light chain comprising the sequence of SEQ ID NO: 79 and a heavy chain comprising the sequence of SEQ ID NO: 133.

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

12. The isolated antibody or antigen-binding fragment of any one of claims 1 to 6, wherein the isolated antibody or antigen-binding fragment is selected from the group consisting of a Fab fragment, an Fab' fragment, an F(ab')2 fragment, an Fv fragment, a diabody, and a single chain antibody.

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

14. The isolated antibody or antigen-binding fragment thereof of claim 13, wherein the antibody is a fully human monoclonal antibody.

15. The isolated antibody or antigen-binding fragment thereof of claim 11, wherein the antibody is an IgG1-, IgG2-, IgG3-, or IgG4-type antibody.

16. The isolated antibody or antigen-binding fragment thereof of claim 15, wherein the antibody is an aglycosylated IgG1 antibody.

17. The isolated antibody or antigen-binding fragment thereof of claim 16, wherein the antibody comprises a mutation at position N297 in its heavy chain.

18. The isolated antibody or antigen-binding fragment thereof of claim 17, wherein the antibody comprises a N297G mutation in its heavy chain.

19. The isolated antibody or antigen-binding fragment thereof of claim 17, wherein the antibody further comprises R292C and V302C mutations in its heavy chain.

20. An isolated polynucleotide that encodes an antibody or antigen-binding fragment thereof of any one of claims 1 to 19.

21. An expression vector comprising the polynucleotide of claim 20.

22. A cell line transformed with the expression vector of claim 21.

23. A method of making an antibody or antigen-binding fragment thereof of any one of claims 1 to 19, comprising preparing the antibody or antigen-binding fragment thereof from the cell line of claim 22 that secretes the antibody or antigen-binding fragment thereof.

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

25. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 19 in the manufacture of a medicament for treating headache in a patient.

26. The use of claim 25, wherein the headache is migraine.

27. The use of claim 26, wherein the migraine is episodic migraine or chronic migraine.

28. The use of claim 25, wherein the headache is cluster headache.

29. The use of any of claims 25 to 28, wherein the treating comprises prophylactic treatment.