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 PAC1, comprising (A) a light chain CDR1 (CDRL1) comprising the sequence of SEQ ID NO: 196, SEQ ID NO: 197, or SEQ ID NO: 208; (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, SEQ ID NO: 225, or SEQ ID NO: 233; (E) a heavy chain CDR2 (CDRH2) comprising the sequence of SEQ ID NO: 237 or SEQ ID NO: 238; and (F) a heavy chain CDR3 (CDRH3) comprising the sequence of SEQ ID NO: 246, SEQ ID NO: 247, or SEQ ID NO: 250. 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 a condition associated with PAC1 in a patient. In one example, the ~~invention~~ 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

4A, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the LC CDR3 sequences set forth in Table 4A.

In another ~~aspect~~example, the ~~invention~~ disclosure includes an antibody or antigen binding fragment thereof, wherein (A) the antibody or antigen binding fragment thereof competes for binding, with a Ki of 10 nM or less (e.g., 5 nM or 1 nM), to human PAC1 with a reference antibody, said reference antibody selected from the group consisting of 01B, 14A, 14B, 26A, 26B, 28A, 29A, 29B, 39A, and39B; and (B) the antibody or antigen binding fragment thereof specifically binds human PAC1.

In another example~~aspect~~, the disclosure~~invention~~ includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising: (A) a heavy chain CDR1 comprising (i) an amino acid sequence selected from the group consisting of the HC CDR1 sequences set forth in Table 4B, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the HC CDR1 sequences set forth in Table 4B, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the HC CDR1 sequences set forth in Table 4B; (B) a heavy chain CDR2 comprising (i) an amino acid sequence selected from the group consisting of the HC CDR2 sequences set forth in Table 4B, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the HC CDR2 sequences set forth in Table 4B, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the HC CDR2 sequences set forth in Table 4B; and (C) a heavy chain CDR3 comprising (i) an amino acid sequence selected from the group consisting of the HC CDR3 sequences set forth in Table 4B, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the HC CDR3 sequences set forth in Table 4B, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the HC CDR3 sequences set forth in Table 4B.

In another ~~aspect~~example, the ~~invention~~disclosure includes an antibody or antigen binding fragment thereof, wherein (A) the CDRLs comprise (i) a CDRL1 selected from the group consisting of CDRL1-C1 and CDRL1-C2, (ii) a CDRL2 selected from the group consisting of CDRL2-C1, CDRL2-C2, and CDRL2-C3, and (iii) a CDRL3 consisting of CDRL3-C1; (B) the CDRHs comprise (i) a CDRH1 selected from the group consisting of CDRH1-C1 and CDRH1-C2; (ii) a CDRH2 selected from the group consisting of CDRH2-C1, CDRH2-C2, and CDRH2-C3; and (iii) a CDRH3 consisting of CDRH3-C1, and (C) the antibody or antigen binding fragment thereof specifically binds human PAC1.

In one ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C1, CDRL3-C1, CDRH1-C1, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C1, CDRL3-C1, CDRH1-C1, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C1, CDRL3-C1, CDRH1-C1, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C1, CDRL3-C1, CDRH1-C2, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C1, CDRL3-C1, CDRH1-C2, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C1, CDRL3-C1, CDRH1-C2, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C2, CDRL3-C1, CDRH1-C1, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C2, CDRL3-C1, CDRH1-C1, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C2, CDRL3-C1, CDRH1-C1, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C2, CDRL3-C1, CDRH1-C2, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C2, CDRL3-C1, CDRH1-C2, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C2, CDRL3-C1, CDRH1-C2, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C3, CDRL3-C1, CDRH1-C1, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C3, CDRL3-C1, CDRH1-C1, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C3, CDRL3-C1, CDRH1-C1, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C3, CDRL3-C1, CDRH1-C2, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C3, CDRL3-C1, CDRH1-C2, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C1, CDRL2-C3, CDRL3-C1, CDRH1-C2, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C1, CDRL3-C1, CDRH1-C1, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C1, CDRL3-C1, CDRH1-C1, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C1, CDRL3-C1, CDRH1-C1, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C1, CDRL3-C1, CDRH1-C2, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C1, CDRL3-C1, CDRH1-C2, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C1, CDRL3-C1, CDRH1-C2, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C2, CDRL3-C1, CDRH1-C1, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C2, CDRL3-C1, CDRH1-C1, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C2, CDRL3-C1, CDRH1-C1, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C2, CDRL3-C1, CDRH1-C2, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C2, CDRL3-C1, CDRH1-C2, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C2, CDRL3-C1, CDRH1-C2, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C3, CDRL3-C1, CDRH1-C1, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C3, CDRL3-C1, CDRH1-C1, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C3, CDRL3-C1, CDRH1-C1, CDRH2-C3, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C3, CDRL3-C1, CDRH1-C2, CDRH2-C1, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C3, CDRL3-C1, CDRH1-C2, CDRH2-C2, and CDRH3-C1.

In another ~~embodiment~~example of the above, the antibody or antigen binding fragment thereof comprises CDRL1-C2, CDRL2-C3, CDRL3-C1, CDRH1-C2, CDRH2-C3, and CDRH3-C1.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising (i) heavy chain CDRs CDR1, CDR2 and CDR3, each having a sequence of the corresponding heavy chain CDR as above, and (ii) light chain CDRs CDR1, CDR2 and CDR3, each having a sequence of the corresponding heavy chain CDR as above.

In one ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-8, CDRH2-2 and CDRH3-3; and light chain CDRs: CDRL1-3, CDRL2-2, CDRL3-2.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-11, CDRH2-5 and CDRH3-9; and light chain CDRs: CDRL1-13, CDRL2-1, CDRL3-1.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-1, CDRH2-4 and CDRH3-6; and light chain CDRs: CDRL1-2, CDRL2-1, CDRL3-1.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-1, CDRH2-4 and CDRH3-6; and light chain CDRs: CDRL1-1, CDRL2-1, CDRL3-1.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-3, CDRH2-5 and CDRH3-5; and light chain CDRs: CDRL1-1, CDRL2-1, CDRL3-1.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-9, CDRH2-6 and CDRH3-1; and light chain CDRs: CDRL1-4, CDRL2-3, CDRL3-3.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-4, CDRH2-7 and CDRH3-8; and light chain CDRs: CDRL1-6, CDRL2-4, CDRL3-5.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-10, CDRH2-1 and CDRH3-7; and light chain CDRs: CDRL1-5, CDRL2-3, CDRL3-4.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-6, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-7, CDRL2-5, CDRL3-6.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-7, CDRH2-3 and CDRH3-4; and light chain CDRs: CDRL1-8, CDRL2-6, CDRL3-7.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-2, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-9, CDRL2-5, CDRL3-8.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-6, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-10, CDRL2-5, CDRL3-6.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-6, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-10, CDRL2-5, CDRL3-6.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-6, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-12, CDRL2-5, CDRL3-6.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising heavy chain CDRs: CDRH1-5, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-11, CDRL2-5, CDRL3-8.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a heavy chain CDR1 selected from the group consisting of CDRH1-1, CDRH1-2, CDRH1-3, CDRH1-4, CDRH1-5, CDRH1-6, CDRH1-7, CDRH1-8, CDRH1-9, CDRH1-10, and CDRH1-11.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a heavy chain CDR2 selected from the group consisting of CDRH2-1, CDRH2-2, CDRH2-3, CDRH2-4, CDRH2-5, CDRH2-6, CDRH2-7, and CDRH2-8.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a heavy chain CDR3 selected from the group consisting of CDRH3-1, CDRH3-2, CDRH3-3, CDRH3-4, CDRH3-5, CDRH3-6, CDRH3-7, CDRH3-8 and CDRH3-9.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a light chain CDR1 selected from the group consisting of CDRL1-1, CDRL1-2, CDRL1-3, CDRL1-4, CDRL1-5, CDRL1-6, CDRL1-7, CDRL1-8, CDRL1-9, CDRL1-10, CDRL1-11, CDRL1-12 and CDRL1-13.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a light chain CDR2 selected from the group consisting of CDRL2-1, CDRL2-2, CDRL2-3, CDRL2-4, CDRL2-5, and CDRL2-6.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a light chain CDR3 selected from the group consisting of CDRL3-1, CDRL3-2, CDRL3-3, CDRL3-4, CDRL3-5, CDRL3-6, CDRL3-7, and CDRL3-8.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that optionally specifically binds human PAC1, comprising a heavy chain CDR1 as above, a heavy chain CDR2 as above, a heavy chain CDR3 as above, a light chain CDR1 as above, a light chain CDR2 as above, and a light chain CDR3 as above.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that optionally specifically binds human PAC1, comprising a light chain variable region comprising (i) an amino acid sequence selected from the group consisting of the V_L AA sequences set forth in Table 3A, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the V_L AA sequences set forth in Table 3A, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the V_L AA sequences set forth in Table 3A.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a heavy chain variable region comprising (i) an amino acid sequence selected from the group consisting of the V_H AA sequences set forth in Table 3B, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the V_H AA sequences set forth in Table 3B, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the V_H AA sequences set forth in Table 3B.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a light chain variable region amino acid sequence selected from the group consisting of LV-01, LV-02, LV-03, LV-04, LV-05, LV-06, LV-07, LV-08, LV-09, LV-10, LV-11, LV-12, LV-13, LV-14, LV-15, LV-16, LV-17, LV-18, LV-19, LV-20, and LV-21.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a heavy chain variable region amino acid sequence selected from the group consisting of HV-01, HV-02, HV-03, HV-04, HV-05, HV-06, HV-07, HV-08, HV-09, HV-10, HV-11, HV-12, HV-13, HV-14, HV-15, HV-16, HV-17, HV-18, HV-19, HV-20, HV-21, HV-22, HV-23, HV-24, HV-25, and HV-26.

In one ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-01 and HV-01.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-02 and HV-02.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-03 and HV-02.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-04 and HV-03.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-03.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-06 and HV-03.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-04 and HV-04.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-04 and HV-05.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-07 and HV-04.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-07 and HV-05.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-07 and HV-03.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-04 and HV-06.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-04 and HV-06.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-05.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-08 and HV-05.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-09 and HV-05.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-07.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-08.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-09 and HV-07.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-09 and HV-08.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-09 and HV-09.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-09.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-10.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-08 and HV-10.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-11.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-12.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-05 and HV-13.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-08 and HV-13.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-10 and HV-14.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-11 and HV-14.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-12 and HV-15.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-12 and HV-16.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-13 and HV-17.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-14 and HV-18.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-14 and HV-19.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-15 and HV-20.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-16 and HV-21.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-17 and HV-22.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-18 and HV-23.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-19 and HV-24.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-19 and HV-25.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-20 and HV-21.

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LV-21 and HV-26.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a (i) a sequence selected from the group consisting of the sequences set forth in Table 2A, or (ii) a sequence at least 90% identical to one of the sequences in set forth in Table 2A, or (iii) a sequence at least 95% identical to one of the sequences in set forth in Table 2A.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a (i) a sequence selected from the group consisting of the sequences set forth in Table 2B, or (ii) a sequence at least 90% identical to one of the sequences in set forth in Table 2B, or (iii) a sequence at least 95% identical to one of the sequences in set forth in Table 2B.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a light chain amino acid sequence selected from the group consisting of LC-01, LC-02, LC-03, LC-04, LC-05, LC-06, LC-07, LC-08, LC-09, LC-10, LC-11, LC-12, LC-13, LC-14, LC-15, LC-16, LC-17, LC-18, LC-19, LC-20, and LC-21.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a heavy chain amino acid sequence selected from the group consisting of HC-01, HC-02, HC-03, HC-04, HC-05, HC-06, HC-07, HC-08, HC-09, HC-10, HC-11, HC-12, HC-13, HC-14, HC-15, HC-16, HC-17, HC-18, HC-19, HC-20, HC-21, HC-22, HC-23, HC-24, HC-25, HC-26, HC-27, HC-28, HC-29, HC-30, HC-31, HC-32, HC-33, HC-34, HC-35, HC-36, HC-37, HC-38, HC-39, HC-40, HC-41, HC-42, HC-43, HC-44, HC-45, HC-46, HC-47, HC-48, HC-49, HC-50, HC-51, HC-52, and HC-53.

In one ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-01 and HC-01 (01A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-01 and HC-02 (01B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-02 and HC-03 (02A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-02 and HC-04 (02B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-02 and HC-05 (02C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-03 and HC-03 (03A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-06 (04A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-07 (04B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-08 (04C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-06 (05A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-07 (05B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-08 (05C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-06 and HC-06 (06A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-06 and HC-07 (06B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-06 and HC-08 (06C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-09 (07A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-10 (07B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-11 (07C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-12 (08A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-13 (08B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-14 (08C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-09 (09A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-10 (09B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-11 (09C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-12 (10A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-13 (10B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-14 (10C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-06 (11A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-07 (11B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-07 and HC-08 (11C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-15 (12A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-16 (12B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-04 and HC-17 (12C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-12 (13A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-13 (13B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-14 (13C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-12 (14A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-13 (14B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-14 (14C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-12 (15A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-13 (15B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-14 (15C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-18 (16A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-19 (16B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-20 (16C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-21 (17A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-22 (17B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-23 (17C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-18 (18A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-19 (18B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-20 (18C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-21 (19A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-22 (19B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-23 (19C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-24 (20A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-25 (20B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-09 and HC-26 (20C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-24 (21A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-25 (21B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-26 (21C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-27 (22A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-28 (22B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-29 (22C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-27 (23A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-28 (23B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-29 (23C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-30 (24A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-31 (24B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-32 (24C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-33 (25A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-34 (25B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-35 (25C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-36 (26A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-37 (26B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-05 and HC-38 (26C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-36 (27A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-37 (27B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-08 and HC-38 (27C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-10 and HC-39 (28A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-10 and HC-40 (28B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-10 and HC-41 (28C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-11 and HC-39 (29A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-11 and HC-40 (29B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-11 and HC-41 (29C).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-12 and HC-42 (30A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-12 and HC-43 (31A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-13 and HC-44 (32A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-14 and HC-45 (33A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-14 and HC-46 (34A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-15 and HC-47 (35A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-16 and HC-48 (36A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-17 and HC-49 (37A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-18 and HC-50 (38A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-19 and HC-51 (39A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-19 and HC-52 (39B).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-20 and HC-48 (40A).

In another ~~embodiment~~example the ~~invention~~disclosure includes an antibody or antigen-binding fragment thereof, comprising LC-21 and HC-53 (41A).

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated antibody or antigen-binding fragment thereof of any of the foregoing, wherein the antibody is a polyclonal antibody.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody of any of the above, wherein the isolated antibody is selected from the group consisting of a monoclonal antibody, a Fab fragment, an Fab' fragment, an F(ab')2 fragment, an Fv fragment, a diabody, and a single chain antibody.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the isolated antibody is a monoclonal antibody selected from the group consisting of a fully human antibody, a humanized antibody and a chimeric antibody.

In one ~~embodiment~~example of the above, the isolated antibody according to any of the above is a fully human monoclonal antibody.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the antibody is an IgG1-, IgG2-, IgG3-, or IgG4-type antibody.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the antibody is an aglycosylated IgG1 antibody.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the aglycosylated IgG1 antibody comprises a mutation at position N297 in its heavy chain.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the aglycosylated IgG1 antibody comprises the substitution N297G in its heavy chain.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the aglycosylated IgG1 antibody comprises the substitutions N297G, R292C and V302C in its heavy chain.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody of any as above, wherein the antibody selectively inhibits hPAC1 relative to hVPA1 and hVPAC2.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the selectivity ratio is greater than 100:1.

In another ~~aspect~~example, the ~~invention~~disclosure includes the isolated antibody as above, wherein the selectivity ratio is greater than 1000:1.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated polynucleotide that encodes an antibody of any as above.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated nucleic acid encoding an antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising (i) a sequence

selected from the group consisting of the sequences set forth in Table 1A, or (ii) a sequence at least 90% identical to one of the sequences in set forth in Table 1A, or (iii) a sequence at least 95% identical to one of the sequences in set forth in Table 1A.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated nucleic acid encoding an antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising (i) a sequence selected from the group consisting of the sequences set forth in Table 1B, or (ii) a sequence at least 90% identical to one of the sequences in set forth in Table 1B, or (iii) a sequence at least 95% identical to one of the sequences in set forth in Table 1B.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated polynucleotide having a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1A, (ii) a nucleic acid sequence at least 80% identical to a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1A, (iii) a nucleic acid sequence at least 90% identical to a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1A, or (iv) a nucleic acid sequence at least 95% identical to a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1A.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated polynucleotide having a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1B, (ii) a nucleic acid sequence at least 80% identical to a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1B, (iii) a nucleic acid sequence at least 90% identical to a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1B, or (iv) a nucleic acid sequence at least 95% identical to a nucleic acid sequence selected from the group consisting of the sequences set forth in Table 1B.

In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated polynucleotide having a nucleic acid sequence selected from the group consisting of nucleic acid sequences encoding the variable regions set forth in Table 3A, (ii) a nucleic acid sequence at least 80% identical to a nucleic acid sequence selected from the group consisting of nucleic acid sequences encoding the variable regions set forth in Table 3A, (iii) a nucleic acid sequence at least 90% identical to a nucleic acid sequence selected from the group consisting of nucleic acid sequences encoding the variable regions set forth in Table 3A, or (iv) a nucleic acid sequence at least 95% identical to a nucleic acid sequence selected from the group consisting of nucleic acid sequences encoding the variable regions set forth in Table 3A. In another ~~aspect~~example, the ~~invention~~disclosure includes an isolated polynucleotide having a nucleic acid sequence selected from the group consisting of nucleic acid sequences encoding the variable regions set forth in Table 3B, (ii) a nucleic acid sequence at least 80% identical to a nucleic acid sequence selected from the group consisting of nucleic acid sequences

encoding the variable regions set forth in Table 3B, (iii) a nucleic acid sequence at least 90% identical to a nucleic acid sequence selected from the group consisting of nucleic acid sequences encoding the variable regions set forth in Table 3B, or (iv) a nucleic acid sequence at least 95% identical to a nucleic acid sequence selected from the group consisting of nucleic acid sequences encoding the variable regions set forth in Table 3A.

In another ~~aspect~~example, the ~~invention~~disclosure includes an expression vector comprising an isolated nucleic acid or polynucleotide of any as above.

In another ~~aspect~~example, the ~~invention~~disclosure includes a cell line transformed with expression vector as above.

In another ~~aspect~~example, the ~~invention~~disclosure includes a method of making an antibody or antigen binding fragment thereof of any as above, comprising preparing the antibody or antigen binding fragment thereof from a host cell as above that secretes the antibody or antigen binding fragment thereof.

In another ~~aspect~~example, the ~~invention~~disclosure includes a pharmaceutical composition comprising an antibody or antigen binding fragment thereof of any as above and a pharmaceutically acceptable excipient.

In another ~~aspect~~example, the ~~invention~~disclosure includes a method for treating a condition associated with PAC1 in a patient, comprising administering to a patient an effective amount of an antibody or antigen binding fragment thereof of any as above.

In another ~~aspect~~example, the ~~invention~~disclosure includes the method as above, wherein the condition is headache.

In another ~~aspect~~example, the ~~invention~~disclosure includes the method as above, wherein the condition is migraine.

In another ~~aspect~~example, the ~~invention~~disclosure includes the method as above, wherein the migraine is episodic migraine.

In another ~~aspect~~example, the ~~invention~~disclosure includes the method as above, wherein the migraine is chronic migraine.

In another ~~aspect~~example, the ~~invention~~disclosure includes the method as above, wherein the condition is cluster headache.

In another ~~aspect~~example, the ~~invention~~disclosure includes the method of any as above, wherein the method comprises prophylactic treatment.

BRIEF DESCRIPTION OF THE FIGURES

Claims:

1. 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;

(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 4A, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the LC CDR3 sequences set forth in Table 4A;

(D) a heavy chain CDR1 comprising (i) an amino acid sequence selected from the group consisting of the HC CDR1 sequences set forth in Table 4B, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the HC CDR1 sequences set forth in Table 4B, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the HC CDR1 sequences set forth in Table 4B;

(E) a heavy chain CDR2 comprising (i) an amino acid sequence selected from the group consisting of the HC CDR2 sequences set forth in Table 4B, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the HC CDR2 sequences set forth in Table 4B, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the HC CDR2 sequences set forth in Table 4B; and

(F) a heavy chain CDR3 comprising (i) an amino acid sequence selected from the group consisting of the HC CDR3 sequences set forth in Table 4B, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the HC CDR3 sequences set forth in Table 4B, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the HC CDR3 sequences set forth in Table 4B.

2. An isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising a light chain variable region comprising (i) an amino acid sequence selected from the group consisting of the V_L AA sequences set forth in Table 3A, (ii) an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of the V_L AA sequences set forth in Table 3A, or (iii) an amino acid sequence at least 95% identical to an amino acid sequence selected from the group consisting of the V_L AA sequences set forth in Table 3A.

3. An isolated antibody or antigen-binding fragment thereof, comprising amino acid sequences LV-01 and HV-01; LV-02 and HV-02; LV-03 and HV-02; LV-04 and HV-03; LV-05 and HV-03; LV-06 and HV-03; LV-04 and HV-04; LV-04 and HV-05; LV-07 and HV-04; LV-07 and HV-05; LV-07 and HV-03; LV-04 and HV-06; LV-04 and HV-06; LV-05 and HV-05; LV-08 and HV-05; LV-09 and HV-05; LV-05 and HV-07; LV-05 and HV-08; LV-09 and HV-07; LV-09 and HV-08; LV-09 and HV-09; LV-05 and HV-09; LV-05 and HV-10; LV-08 and HV-10; LV-05 and HV-11; LV-05 and HV-12; LV-05 and HV-13; LV-08 and HV-13; LV-10 and HV-14; LV-11 and HV-14; LV-12 and HV-15; LV-12 and HV-16; LV-13 and HV-17; LV-14 and HV-18; LV-14 and HV-19; LV-15 and HV-20; LV-16 and HV-21; LV-17 and HV-22; LV-18 and HV-23; LV-19 and HV-24; LV-19 and HV-25; LV-20 and HV-21; or LV-21 and HV-26; wherein said antibody or antigen-binding fragment thereof binds selectively to hPAC1.

4. An isolated antibody or antigen-binding fragment thereof, comprising amino acid sequences LC-01 and HC-01 (01A); LC-01 and HC-02 (01B); LC-02 and HC-03 (02A); LC-02 and HC-04 (02B); LC-02 and HC-05 (02C); LC-03 and HC-03 (03A); LC-04 and HC-06 (04A); LC-04 and HC-07 (04B); LC-04 and HC-08 (04C); LC-05 and HC-06 (05A); LC-05 and HC-07 (05B); LC-05 and HC-08 (05C); LC-06 and HC-06 (06A); LC-06 and HC-07 (06B); LC-06 and HC-08 (06C); LC-04 and HC-09 (07A); LC-04 and HC-10 (07B); LC-04 and HC-11 (07C); LC-04 and HC-12 (08A); LC-04 and HC-13 (08B); LC-04 and HC-14 (08C); LC-07 and HC-09 (09A); LC-07 and HC-10 (09B); LC-07 and HC-11 (09C); LC-07 and HC-12 (10A); LC-07 and

HC-13 (10B); LC-07 and HC-14 (10C); LC-07 and HC-06 (11A); LC-07 and HC-07 (11B); LC-07 and HC-08 (11C); LC-04 and HC-15 (12A); LC-04 and HC-16 (12B); LC-04 and HC-17 (12C); LC-05 and HC-12 (13A); LC-05 and HC-13 (13B); LC-05 and HC-14 (13C); LC-08 and HC-12 (14A); LC-08 and HC-13 (14B); LC-08 and HC-14 (14C); LC-09 and HC-12 (15A); LC-09 and HC-13 (15B); LC-09 and HC-14 (15C); LC-05 and HC-18 (16A); LC-05 and HC-19 (16B); LC-05 and HC-20 (16C); LC-05 and HC-21 (17A); LC-05 and HC-22 (17B); LC-05 and HC-23 (17C); LC-09 and HC-18 (18A); LC-09 and HC-19 (18B); LC-09 and HC-20 (18C); LC-09 and HC-21 (19A); LC-09 and HC-22 (19B); LC-09 and HC-23 (19C); LC-09 and HC-24 (20A); LC-09 and HC-25 (20B); LC-09 and HC-26 (20C); LC-05 and HC-24 (21A); LC-05 and HC-25 (21B); LC-05 and HC-26 (21C); LC-05 and HC-27 (22A); LC-05 and HC-28 (22B); LC-05 and HC-29 (22C); LC-08 and HC-27 (23A); LC-08 and HC-28 (23B); LC-08 and HC-29 (23C); LC-05 and HC-30 (24A); LC-05 and HC-31 (24B); LC-05 and HC-32 (24C); LC-05 and HC-33 (25A); LC-05 and HC-34 (25B); LC-05 and HC-35 (25C); LC-05 and HC-36 (26A); LC-05 and HC-37 (26B); LC-05 and HC-38 (26C); LC-08 and HC-36 (27A); LC-08 and HC-37 (27B); LC-08 and HC-38 (27C); LC-10 and HC-39 (28A); LC-10 and HC-40 (28B); LC-10 and HC-41 (28C); LC-11 and HC-39 (29A); LC-11 and HC-40 (29B); LC-11 and HC-41 (29C); LC-12 and HC-42 (30A); LC-12 and HC-43 (31A); LC-13 and HC-44 (32A); LC-14 and HC-45 (33A); LC-14 and HC-46 (34A); LC-15 and HC-47 (35A); LC-16 and HC-48 (36A); LC-17 and HC-49 (37A); LC-18 and HC-50 (38A); LC-19 and HC-51 (39A); LC-19 and HC-52 (39B); LC-20 and HC-48 (40A); or LC-21 and HC-53 (41A); wherein said antibody or antigen-binding fragment thereof binds selectively to hPAC1.

5. An isolated antibody or antigen-binding fragment thereof, comprising

heavy chain CDRs: CDRH1-8, CDRH2-2 and CDRH3-3; and light chain CDRs: CDRL1-3, CDRL2-2, CDRL3-2,

heavy chain CDRs: CDRH1-11, CDRH2-5 and CDRH3-9; and light chain CDRs: CDRL1-13, CDRL2-1, CDRL3-1,

heavy chain CDRs: CDRH1-1, CDRH2-4 and CDRH3-6; and light chain CDRs: CDRL1-2, CDRL2-1, CDRL3-1,

heavy chain CDRs: CDRH1-1, CDRH2-4 and CDRH3-6; and light chain CDRs: CDRL1-1, CDRL2-1, CDRL3-1,

heavy chain CDRs: CDRH1-3, CDRH2-5 and CDRH3-5; and light chain CDRs: CDRL1-1, CDRL2-1, CDRL3-1,

heavy chain CDRs: CDRH1-9, CDRH2-6 and CDRH3-1; and light chain CDRs: CDRL1-4, CDRL2-3, CDRL3-3,

heavy chain CDRs: CDRH1-4, CDRH2-7 and CDRH3-8; and light chain CDRs: CDRL1-6, CDRL2-4, CDRL3-5,

heavy chain CDRs: CDRH1-10, CDRH2-1 and CDRH3-7; and light chain CDRs: CDRL1-5, CDRL2-3, CDRL3-4,

heavy chain CDRs: CDRH1-6, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-7, CDRL2-5, CDRL3-6,

heavy chain CDRs: CDRH1-7, CDRH2-3 and CDRH3-4; and light chain CDRs: CDRL1-8, CDRL2-6, CDRL3-7,

heavy chain CDRs: CDRH1-2, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-9, CDRL2-5, CDRL3-8,

heavy chain CDRs: CDRH1-6, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-10, CDRL2-5, CDRL3-6,

heavy chain CDRs: CDRH1-6, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-12, CDRL2-5, CDRL3-6, or

heavy chain CDRs: CDRH1-5, CDRH2-8 and CDRH3-2; and light chain CDRs: CDRL1-11, CDRL2-5, CDRL3-8,

wherein said antibody or antigen-binding fragment thereof binds selectively to hPAC1.

6. An antibody or antigen binding fragment thereof, wherein

(A) the antibody or antigen binding fragment thereof competes for binding, with a Ki of 100 nM or less (e.g., 50 nM), to human PAC1 with a reference antibody, said reference antibody selected from the group consisting of 01B, 14A, 14B, 26A, 26B, 28A, 29A, 29B, 39A, and39B; and

(B) the antibody or antigen binding fragment thereof binds selectively to human PAC1.

7. An antibody or antigen binding fragment thereof, wherein

(A) the CDRLs are selected from the group consisting of: (i) a CDRL1 selected from the group consisting of CDRL1-C1 and CDRL1-C2, (ii) a CDRL2 selected from the group consisting of CDRL2-C1, CDRL2-C2, and CDRL2-C3, and (iii) a CDRL3 consisting of CDRL3-C1;

(B) the CDRHs are selected from the group consisting of: (i) a CDRH1 selected from the group consisting of CDRH1-C1 and CDRH1-C2; (ii) a CDRH2 selected from the group consisting of CDRH2-C1, CDRH2-C2, and CDRH2-C3; and (iii) a CDRH3 consisting of CDRH3-C1, and

(C) the antibody or antigen binding fragment thereof selectively binds human PAC1.

8. An isolated antibody or antigen-binding fragment thereof of any of claims 1-7, wherein the antibody is a monoclonal antibody.

9. The isolated antibody of any of claims 1 -8, wherein the isolated antibody is selected from the group consisting of a monoclonal antibody, a Fab fragment, an Fab' fragment, an F(ab')2 fragment, an Fv fragment, a diabody, and a single chain antibody.

10. The isolated antibody of claim 9, wherein the monoclonal antibody is selected from the group consisting of a fully human antibody, a humanized antibody and a chimeric antibody.

11. The isolated antibody of claim 10, wherein the isolated antibody is a fully human monoclonal antibody.

12. The isolated antibody of claim 8, wherein the antibody is an IgG1-, IgG2-, IgG3-, or IgG4-type antibody.

13. The isolated antibody of claim 12, wherein the antibody is an aglycosylated IgG1 antibody.

14. The isolated antibody of claim 13, wherein the antibody comprises an N297 mutation in its heavy chain.

15. The isolated antibody of claim 14, wherein the antibody comprises an N297G substitution in its heavy chain.

16. The isolated antibody of claim 14, wherein the antibody further comprises the substitutions R292C and V302C in its heavy chain.

17. The isolated antibody of any of claims 1-16, wherein the antibody selectively inhibits hPAC1 relative to VPA1 and VPAC2.

18. The isolated antibody of claim 17, wherein the selectivity ratio is greater than 100:1.

19. The isolated antibody of claim 18, wherein the selectivity ratio is greater than 1000:1.

20. An isolated polynucleotide that encodes an antibody of any of claims 1-19.

21. An expression vector comprising an isolated nucleic acid or polynucleotide of claim 20.

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

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

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

25. A method for treating a condition associated with PAC1 in a patient, comprising administering to a patient an effective amount of an antibody or antigen binding fragment thereof of any of claims 1-19.

26. The method of claim 25, wherein the condition is headache.

27. The method of claim 26, wherein the condition is migraine.

28. The method of claim 27, wherein the migraine is episodic migraine or chronic migraine.

29. The method of claim 26, wherein the condition is cluster headache.

30. The method of any of claims 25 to 29, wherein the method comprises prophylactic treatment.

Claims:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds human PAC1, comprising

(A) a light chain CDR1 (CDRL1) comprising the sequence of SEQ ID NO: 196, SEQ ID NO: 197, or SEQ ID NO: 208;

(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, SEQ ID NO: 225, or SEQ ID NO: 233;

(E) a heavy chain CDR2 (CDRH2) comprising the sequence of SEQ ID NO: 237 or SEQ ID NO: 238; and

(F) a heavy chain CDR3 (CDRH3) comprising the sequence of SEQ ID NO: 246, SEQ ID NO: 247, or SEQ ID NO: 250.

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

(a) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NO: 233, SEQ ID NO: 238, and SEQ ID NO: 250, respectively, and CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NO: 208, SEQ ID NO: 209, and SEQ ID NO: 215, respectively;

(b) 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;

(c) 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; or

(d) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NO: 225, SEQ ID NO: 238, and SEQ ID NO: 246, respectively and CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NO: 196, SEQ ID NO: 209, and SEQ ID NO: 215, respectively.

3. The isolated antibody or antigen-binding fragment thereof of claim 2, 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: 150-159 and the heavy chain variable region comprises a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 171-183.

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: 150 and the heavy chain variable region comprises the sequence of SEQ ID NO: 171;

(b) the light chain variable region comprises the sequence of SEQ ID NO: 151 and the heavy chain variable region comprises the sequence of SEQ ID NO: 171;

(c) 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;

(d) 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;

(e) 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;

(f) 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;

(g) 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;

(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: 173;

(i) 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;

(j) 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;

(k) 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;

(l) 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;

(m) 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;

(n) 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;

(o) 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;

(p) 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;

(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: 176;

(r) 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;

(s) 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;

(t) 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;

(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: 179;

(v) 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;

(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: 180;

(x) 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;

(y) 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;

(z) 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;

(aa) the light chain variable region comprises the sequence of SEQ ID NO: 158 and the heavy chain variable region comprises the sequence of SEQ ID NO: 183; or

(ab) the light chain variable region comprises the sequence of SEQ ID NO: 159 and the heavy chain variable region comprises the sequence of SEQ ID NO: 183.

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: 76 and a heavy chain comprising a sequence selected from SEQ ID NOs: 98-100;

(b) a light chain comprising the sequence of SEQ ID NO: 77 and a heavy chain comprising the sequence of SEQ ID NO: 98;

(c) 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;

(d) 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;

(e) 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;

(f) 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;

(g) 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;

(h) 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;

(i) a light chain comprising the sequence of SEQ ID NO: 84 and a heavy chain comprising a sequence selected from SEQ ID NOs: 134-136; or

(h) a light chain comprising the sequence of SEQ ID NO: 85 and a heavy chain comprising a sequence selected from SEQ ID NOs: 134-136.

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 7, wherein the antibody is a monoclonal antibody.

12. The isolated antibody or antigen-binding fragment of any one of claims 1 to 7, 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 a condition associated with PAC1 in a patient.

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

27. The use of claim 26, wherein the condition is migraine.

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

29. The use of claim 26, wherein the condition is cluster headache.

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