CLAIMS

1. A single-domain antibody for blocking the calcitonin gene-related peptide (CGRP) pathway, wherein the single-domain antibody comprises a CDR1 as shown in the amino acid sequence of SEQ ID NO: 2, 7, 12, 17, 22, 27, 32, 37, 42, 47, 52, or 57 or any variant thereof, a CDR2 as shown in the amino acid sequence of SEQ ID NO: 3, 8, 13, 18, 23, 28, 33, 38, 43, 48, 53, or 58 or any variant thereof, and a CDR3 as shown in the amino acid sequence of SEQ ID NO: 4, 9, 14, 19, 24, 29, 34, 39, 44, 49, 54, or 59 or any variant thereof;

preferably, the single-domain antibody comprises CDR1 as shown in the amino acid sequence of SEQ ID NO: 12 or any variant thereof, CDR2 as shown in the amino acid sequence of SEQ ID NO: 13 or any variant thereof, and CDR3 as shown in the amino acid sequence of SEQ ID NO: 14 or any variant thereof.

2. The single-domain antibody according to claim 1, wherein the single-domain antibody comprises the CDR1 as shown in the amino acid sequence of SEQ ID NO: 12, the CDR2 as shown in the amino acid sequence of SEQ ID NO: 13, and the CDR3 as shown in the amino acid sequence of SEQ ID NO: 14.

3. The single-domain antibody according to claim 1 or 2, wherein the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 1, 6, 11, 16, 21, 26, 31, 36, 41, 46, 51, 56, 61, 62 or 63 or any variant thereof;

preferably, the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 61, 62, or 63 or any variant thereof;

more preferably, the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 61 or any variant thereof;

preferably, the amino acids in the single-domain antibody have conservative substitutions, and the number of conservatively substituted amino acids does not exceed 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

4. The single-domain antibody according to claim 1 or 2, wherein the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 1, 6, 11, 16, 21, 26, 31, 36, 41, 46, 51, 56, 61, 62 or 63.

5. A fusion protein, which simultaneously blocks the calcitonin gene-related peptide (CGRP) pathway and the pituitary adenylate cyclase-activating peptide (PACAP) pathway, wherein the fusion

protein comprises at least one single-domain antibody, at least one Fc fragment, and at least one extracellular domain fragment of pituitary adenylate cyclase 1 (PAC1 ECD).

6. The fusion protein according to claim 5, wherein the fusion protein comprises one peptide chain, the structure of the peptide chain is that one PAC1 ECD is connected to the C-terminus of an Fc fragment via a linker, and the N-terminus of the Fc fragment is fused to the C-terminus of a single-domain antibody;

optionally, the fusion protein comprises two peptide chains, the structure of the peptide chains is that one PAC1 ECD is connected to the C-terminus of an Fc fragment via a linker, and the N-terminus of the Fc fragment is fused to the C-terminus of a single-domain antibody, and two PAC1 ECDs of the two peptide chains are connected via a linker;

optionally, the fusion protein comprises three peptide chains, the structure of which is that one PAC1 ECD is connected to the C-terminus of an Fc fragment via a linker, and the N-terminus of the Fc fragment is fused to the C-terminus of a single-domain antibody, and three PAC1 ECDs of the three peptide chains are connected via a linker.

7. The fusion protein according to claim 5 or 6, wherein the single-domain antibody is a single-domain antibody that binds to a CGRP receptor;

preferably, the single-domain antibody comprises a CDR1 as shown in the amino acid sequence of SEQ ID NO: 2, 7, 12, 17, 22, 27, 32, 37, 42, 47, 52, or 57 or any variant thereof, a CDR2 as shown in the amino acid sequence of SEQ ID NO: 3, 8, 13, 18, 23, 28, 33, 38, 43, 48, 53, or 58 or any variant thereof, and a CDR3 as shown in the amino acid sequence of SEQ ID NO: 4, 9, 14, 19, 24, 29, 34, 39, 44, 49, 54, or 59 or any variant thereof;

more preferably, the single-domain antibody comprises CDR1 as shown in the amino acid sequence of SEQ ID NO: 12 or any variant thereof, CDR2 as shown in the amino acid sequence of SEQ ID NO: 13 or any variant thereof, and CDR3 as shown in the amino acid sequence of SEQ ID NO: 14 or any variant thereof;

preferably, the amino acids in one or more or all three of the CDRs have conservative substitutions, and the number of conservatively substituted amino acids does not exceed 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

8. The fusion protein according to claim 7, wherein the single-domain antibody comprises the CDR1 as shown in the amino acid sequence of SEQ ID NO: 12, the CDR2 as shown in the amino

acid sequence of SEQ ID NO: 13, and the CDR3 as shown in the amino acid sequence of SEQ ID NO: 14.

9. The fusion protein according to any one of claims 5 to 8, wherein the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 1, 6, 11, 16, 21, 26, 31, 36, 41, 46, 51, 56, 61, 62 or 63 or any variant thereof;

preferably, the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 61, 62, or 63 or any variant thereof;

more preferably, the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 61 or any variant thereof;

preferably, the amino acids in the single-domain antibody have conservative substitutions, and the number of conservatively substituted amino acids does not exceed 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

10. The fusion protein according to any one of claims 5 to 8, wherein the single-domain antibody comprises a variable region as shown in the amino acid sequence of SEQ ID NO: 1, 6, 11, 16, 21, 26, 31, 36, 41, 46, 51, 56, 61, 62 or 63.

11. The fusion protein according to any one of claims 5 to 10, wherein the PAC1 ECD is selected from the ECD of a PAC isoform of PAC1, PAC1s, or PAC1vs;

preferably, the PAC1 ECD is PAC1s ECD.

12. The fusion protein according to claim 11, wherein the PAC1 ECD comprises the amino acid sequence of SEQ ID NO: 64 and an amino acid sequence having 80% or higher identity thereto, preferably an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98%, 99%, or higher identity thereto, and more preferably an amino acid sequence having 98% or 99% or higher identity thereto.

13. The fusion protein according to claim 11, wherein the PAC1 ECD comprises the amino acid sequence of SEQ ID NO: 66 and an amino acid sequence having 80% or higher identity thereto, preferably an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98%, 99%, or higher identity thereto, and more preferably an amino acid sequence having 98% or 99% or higher identity thereto.

14. The fusion protein according to any one of claims 5 to 13, wherein the Fc fragment comprises a hinge region and constant region 2 (CH2) and constant region 3 (CH3) domains derived from a human immunoglobulin;

preferably, the Fc fragment is selected from human IgG1, IgG2, IgG3, and IgG4; more preferably, the Fc fragment is selected to be human IgG1;

preferably, the Fc fragment has an amino acid substitution; more preferably, the amino acid substitution includes replacement of asparagine N at position 297 on the Fc fragment by alanine A, wherein each amino acid site on the Fc fragment is numbered using the EU antibody numbering system;

more preferably, the Fc fragment comprises the amino acid sequence of SEQ ID NO: 68 and an amino acid sequence having 80% or higher identity thereto, preferably an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98%, 99%, or higher identity thereto, and more preferably an amino acid sequence having 98% or 99% or higher identity thereto.

15. The fusion protein according to any one of claims 6 to 14, wherein the linker is a flexible polypeptide linker;

preferably, the flexible polypeptide linker is selected from GGGGS (SEQ ID NO: 79), GGGGSGGGGS (SEQ ID NO: 80), SGGGGSGGGG (SEQ ID NO: 81), GGGGGSGGGGSSGGGGS (SEQ ID NO: 82), GGGGSGGGGSGGGGS (SEQ ID NO: 83), GGGGSGGGGSGGGG, (SEQ ID NO: 84), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 85), GGGGSGGGGSGGGSGGGGS (SEQ ID NO: 86), GSGSGSGS (SEQ ID NO: 87), GGSGSGSG (SEQ ID NO: 88), GGSGSG (SEQ ID NO: 89), and GGSG (SEQ ID NO: 90);

more preferably, the flexible polypeptide linker is GGGGS (SEQ ID NO: 79).

16. A nucleic acid encoding the single-domain antibody according to any one of claims 1 to 4 or the fusion protein according to any one of claims 5 to 15.

17. A vector comprising the nucleic acid according to claim 16.

18. A cell comprising the nucleic acid according to claim 16 or the vector according to claim 17.

19. A pharmaceutical composition or kit comprising the single-domain antibody according to any one of claims 1 to 4 and/or the fusion protein according to any one of claims 5 to 15, as well as a pharmaceutically acceptable vector, diluent, or excipient.

20. Use of the single-domain antibody according to any one of claims 1 to 4, the fusion protein according to any one of claims 5 to 15, the nucleic acid according to claim 16, the vector according

to claim 17, the cell according to claim 18, and/or the pharmaceutical composition or kit according to claim 19 in the manufacture of a medicament for treating a disease associated with activation of the CGRP and PACAP pathways.

21. The use according to claim 20, wherein the disease is migraine.