CLAIMS

1. An anti-adrenomedullin (anti-ADM) monoclonal antibody or a fragment thereof, wherein the monoclonal antibody or the fragment specifically binds to a sequence of amino acids from position 1 to position 21 at the N-terminus of human adrenomedullin (ADM), the sequence of the amino acids from position 1 to position 21 at the N-terminus of the human ADM is set forth in SEQ ID NO: 2, and the monoclonal antibody or the fragment exhibits an affinity for ADM with a KD value of less than 10^{-10} M; preferably, wherein the fragment comprises a Fab, a Fab', an F(ab)2, an Fv fragment, an F(ab')2, a scFv, a di-scFv, a VHH, and/or a dAb.

2. The anti-adrenomedullin monoclonal antibody or the fragment thereof according to claim 1, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTHY (set forth in SEQ ID NO: 55),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DVSILDA (set forth in SEQ ID NO: 56), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTSY (set forth in SEQ ID NO: 43),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTQY (set forth in SEQ ID NO: 51),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASEGISEYLA (set forth in SEQ ID NO: 52),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTQY (set forth in SEQ ID NO: 51),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RAAEGIGSYLA (set forth in SEQ ID NO: 53),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTSY (set forth in SEQ ID NO: 43),

(ii) SPYSGN (set forth in SEQ ID NO: 54), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASEGISEYLA (set forth in SEQ ID NO: 52),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTQY (set forth in SEQ ID NO: 51),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DVSILDA (set forth in SEQ ID NO: 56), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTQY (set forth in SEQ ID NO: 51),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DASNVDT (set forth in SEQ ID NO: 57), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTSY (set forth in SEQ ID NO: 43),

(ii) SPYTGK (set forth in SEQ ID NO: 58), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DVSILDA (set forth in SEQ ID NO: 56), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTSY (set forth in SEQ ID NO: 43),

(ii) SPYTGK (set forth in SEQ ID NO: 58), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DTSDLDT (set forth in SEQ ID NO: 59), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTHY (set forth in SEQ ID NO: 55),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR

sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDDLDLT (set forth in SEQ ID NO: 60);

or, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTQY (set forth in SEQ ID NO: 51),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRWGGSFNI (set forth in SEQ ID NO: 50); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDDLPLS (set forth in SEQ ID NO: 61).

3. The anti-adrenomedullin monoclonal antibody or the fragment thereof according to claim 2, wherein the monoclonal antibody comprises a heavy chain variable region sequence set forth in any one of SEQ ID NOs: 30 to 34, and the monoclonal antibody comprises a light chain variable region sequence set forth in any one of SEQ ID NOs: 35 to 42, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 33 and the light chain variable region sequence set forth in SEQ ID NO: 38, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 30 and the light chain variable region sequence set forth in SEQ ID NO: 35, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 31 and the light chain variable region sequence set forth in SEQ ID NO: 36, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 31 and the light chain variable region sequence set forth in SEQ ID NO: 37, the monoclonal antibody preferably comprises the heavy chain variable region

sequence set forth in SEQ ID NO: 32 and the light chain variable region set forth in SEQ ID NO: 36, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 31 and the light chain variable region sequence set forth in SEQ ID NO: 38, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 31 and the light chain variable region sequence set forth in SEQ ID NO: 39, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 34 and the light chain variable region sequence set forth in SEQ ID NO: 38, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 34 and the light chain variable region sequence set forth in SEQ ID NO: 40, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 33 and the light chain variable region sequence set forth in SEQ ID NO: 41, and the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 31 and the light chain variable region sequence set forth in SEQ ID NO: 42.

4. The anti-adrenomedullin monoclonal antibody or the fragment thereof according to claim 1, wherein:

(a) a heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYAFTTF (set forth in SEQ ID NO: 11),

(ii) NTYSRV (set forth in SEQ ID NO: 12), and

(iii) GYGGEGGLGF (set forth in SEQ ID NO: 13); and

(b) a light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RSSQSIIDSDGNTYLE (set forth in SEQ ID NO: 14),

(ii) KVSNRFS (set forth in SEQ ID NO: 15), and

(iii) FQGSHFPYT (set forth in SEQ ID NO: 16); preferably, wherein the monoclonal antibody comprises a heavy chain variable region sequence set forth in any one of SEQ ID NOs: 9 and 17, and the monoclonal antibody comprises a light chain variable region sequence set forth in

any one of SEQ ID NOs: 10, 18, and 19, wherein the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 9 and the light chain variable region sequence set forth in SEQ ID NO: 10, the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 17 and the light chain variable region sequence set forth in SEQ ID NO: 18, and the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 17 and the light chain variable region sequence set forth in SEQ ID NO: 19;

preferably, wherein the monoclonal antibody comprises a heavy chain sequence set forth in SEQ ID NO: 23 and a light chain sequence set forth in SEQ ID NO: 22;

preferably, wherein the monoclonal antibody comprises a heavy chain sequence set forth in SEQ ID NO: 25 and a light chain sequence set forth in SEQ ID NO: 24;

preferably, wherein the monoclonal antibody comprises a heavy chain sequence set forth in SEQ ID NO: 27 and a light chain sequence set forth in SEQ ID NO: 26.

5. The anti-adrenomedullin monoclonal antibody or the fragment thereof according to claim 1, wherein:

(a) a heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTX$_1$Y, wherein X$_1$ is selected from S, Q, and H,

(ii) SX$_2$YX$_3$GX$_4$, wherein X$_2$ is selected from A and P, X$_3$ is selected from N, Q, S, and T, and X$_4$ is selected from N and K, and

(iii) EGRX$_5$GGSFX$_6$I, wherein X$_5$ is selected from S and W, and X$_6$ is selected from D and N; and

(b) a light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RAX$_7$X$_8$GIX$_9$X$_{10}$YLA, wherein X$_7$ is selected from S and A, X$_8$ is selected from Q and E, X$_9$ is selected from S and G, and X$_{10}$ is selected from S and E,

(ii) DX$_{11}$SX$_{12}$X$_{13}$X$_{14}$X$_{15}$, wherein X$_{11}$ is selected from A, V, and T, X$_{12}$ is selected from N, I, and D, X$_{13}$ is selected from L and V, X$_{14}$ is selected from E and D, and X$_{15}$ is selected from T

and A, and

(iii) $QQYDX_{16}LX_{17}LX_{18}$, wherein X_{16} is selected from N and D, X_{17} is selected from P and D, and X_{18} is selected from T and S preferably, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises sequences of HCDR1, HCDR2, and HCDR3, wherein the HCDR1 comprises an amino acid sequence set forth in any one of SEQ ID NOs: 43, 51, and 55, the HCDR2 comprises an amino acid sequence set forth in any one of SEQ ID NOs: 44, 49, 54, and 58, and the HCDR3 comprises an amino acid sequence set forth in any one of SEQ ID NOs: 45 and 50, and

(b) the light chain variable region of the monoclonal antibody comprises sequences of LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises an amino acid sequence set forth in any one of SEQ ID NOs: 46, 52, and 53, the LCDR2 comprises an amino acid sequence set forth in any one of SEQ ID NOs: 47, 56, 57, and 59, and the LCDR3 comprises an amino acid sequence set forth in any one of SEQ ID NOs: 48, 60, and 61;

preferably, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTSY (set forth in SEQ ID NO: 43),

(ii) SAYNGN (set forth in SEQ ID NO: 44), and

(iii) EGRSGGSFDI (set forth in SEQ ID NO: 45); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48);

preferably, wherein:

(a) the heavy chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) GYTFTSY (set forth in SEQ ID NO: 43),

(ii) SAYQGN (set forth in SEQ ID NO: 49), and

(iii) EGRSGGSFDI (set forth in SEQ ID NO: 45); and

(b) the light chain variable region of the monoclonal antibody comprises the following CDR sequences:

(i) RASQGISSYLA (set forth in SEQ ID NO: 46),

(ii) DASNLET (set forth in SEQ ID NO: 47), and

(iii) QQYDNLPLT (set forth in SEQ ID NO: 48).

6. The anti-adrenomedullin monoclonal antibody or the fragment thereof according to claim 5, wherein the monoclonal antibody comprises a heavy chain variable region sequence set forth in SEQ ID NO: 28 or 29, and the monoclonal antibody comprises a light chain variable region sequence set forth in SEQ ID NO: 35, wherein the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 28 and the light chain variable region sequence set forth in SEQ ID NO: 35, and the monoclonal antibody preferably comprises the heavy chain variable region sequence set forth in SEQ ID NO: 29 and the light chain variable region sequence set forth in SEQ ID NO: 35.

7. A nucleotide sequence encoding the anti-adrenomedullin monoclonal antibody or the fragment thereof according to any one of claims 1 to 6.

8. An expression vector, comprising the nucleotide sequence according to claim 7, wherein preferably, the expression vector is pcDNA3.4.

9. A host cell, comprising the nucleotide sequence according to claim 7 or the expression vector according to claim 8, wherein preferably, the host cell is a CHO cell.

10. A pharmaceutical composition, a detection reagent, or a kit of parts, comprising the anti-adrenomedullin monoclonal antibody or the fragment thereof according to any one of claims 1 to 6.

11. Use of the anti-adrenomedullin monoclonal antibody or the fragment thereof according to any one of claims 1 to 6 for manufacture of a medicament for maintenance of endothelial cell integrity and the enhancement of a barrier function.

12. Use of the anti-adrenomedullin monoclonal antibody or the fragment thereof according to any one of claims 1 to 6 for manufacture of a medicament for controlling vasodilation and lowering blood pressure.

13. Use of the anti-adrenomedullin monoclonal antibody or the fragment thereof according to any one of claims 1 to 6 for manufacture of a medicament for treating or preventing of septic shock or traumatic injury, especially an advanced stage of sepsis.

14. Use of the anti-adrenomedullin monoclonal antibody or the fragment thereof according to any one of claims 1 to 6 for manufacture of a medicament for reduction of death risk in a patient with a chronic or acute disease or an acute condition, wherein the chronic or acute disease or the acute condition is selected from a severe infection such as meningitis, systemic inflammatory response syndrome (SIRS), and septicemia; other diseases such as diabetes, cancers, acute and chronic vascular diseases (such as heart failure, myocardial infarction, stroke, and atherosclerosis), and edema; and shock such as septic shock, organ dysfunction such as renal dysfunction and liver dysfunction, burns, surgery, trauma, and poisoning.

15. Use of the anti-adrenomedullin monoclonal antibody or the fragment thereof according to any one of claims 1 to 6 for manufacture of a medicament for stabilization of circulation, especially systemic circulation, in a patient, wherein the patient suffers from a chronic or acute disease or an acute condition, and the chronic or acute disease or the acute condition is selected from a severe infection such as meningitis, systemic inflammatory response syndrome (SIRS), and septicemia; other diseases such as diabetes, cancers, acute and chronic vascular diseases (such as heart failure, myocardial infarction, stroke, and atherosclerosis), and edema; and shock such as septic shock, organ dysfunction such as renal dysfunction and liver dysfunction, burns,

surgery, trauma, and poisoning.

16. The use according to any one of claims 11 to 15, wherein the anti-adrenomedullin monoclonal antibody or the fragment thereof is used in combination with another medicament;preferably, wherein the medicament is selected from a vasopressor, an intravenous injection, a TNF-α-antibody, and an antibiotic.