Claims

1. Use of an anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold in the manufacture of a medicament for therapy or prevention of shock in a patient, wherein said patient is characterized by having a level of dipeptidyl peptidase 3 (DPP3) in a sample of bodily fluid below a threshold and said anti-ADM antibody or anti-ADM fragment or anti-ADM non-Ig scaffold binds to the N-terminal part (amino acid 1-21) of ADM: YRQSMNNFQGLRSFGCRFGTC (SEQ ID No. 14).

2. The use according to claim 1, wherein said shock is selected from the group comprising shock due to hypovolemia, cardiogenic shock, obstructive shock and distributive shock, in particular cardiogenic shock or septic shock.

3. The use according to claim 1 or 2, wherein
    - in case of cardiogenic shock said patient may have suffered an acute coronary syndrome (e.g. acute myocardial infarction) or wherein said patient has heart failure (e.g. acute decompensated heart failure), myocarditis, arrhythmia, cardiomyopathy, valvular heart disease, aortic dissection with acute aortic stenosis, traumatic chordal rupture or massive pulmonary embolism, or
    - in case of hypovolemic shock said patient may have suffered a hemorrhagic disease including gastrointestinal bleed, trauma, vascular etiologies (e.g. ruptured abdominal aortic aneurysm, tumor eroding into a major blood vessel) and spontaneous bleeding in the setting of anticoagulant use or a non-hemorrhagic disease including vomiting, diarrhea, renal loss, skin losses/insensible losses (e.g. burns, heat stroke) or third-space loss in the setting of pancreatitis, cirrhosis, intestinal obstruction, trauma, or
    - in case of obstructive shock said patient may have suffered a cardiac tamponade, tension pneumothorax, pulmonary embolism or aortic stenosis, or
    - in case of distributive shock said patient may have septic shock, neurogenic shock, anaphylactic shock or shock due to adrenal crisis.

4. The use according to any one of claims 1 to 3, wherein said threshold of DPP3 in a sample of bodily fluid of said patient is between 20 and 120 ng/mL, between 30 and 80 ng/mL, between 40 and 60 ng/mL, or is 50 ng/mL.

5. The use according to claim 4, wherein said threshold of DPP3 in a sample of bodily fluid of said patient is between 40 and 60 ng/mL.

6. The use according to any one of claims 1 to 5, wherein the level of DPP3 is determined by contacting said sample of bodily fluid with a capture binder that binds specifically to DPP3, preferably an antibody.

7. The use according to any one of claims 1 to 6, wherein either the level of DPP3 protein and/or the level of active DPP3 is determined and compared to a predetermined threshold.

8. The use according to any one of claims 1 to 7, wherein said patient is additionally characterized by having a level of ADM-NH_2 above a threshold.

9. The use according to claim 8, wherein said threshold of ADM-NH_2 in a sample of bodily fluid of said patient is between 40 and 100 pg/mL, between 50 and 90 pg/mL, between 60 and 80 pg/mL, or is 70 pg/mL.

10. The use according to claim 9, wherein said threshold of ADM-NH2 in a sample of bodily fluid of said patient is 70 pg/mL.

11. The use according to claims 8-10, wherein the level of ADM-NH_2 is determined by contacting said sample of bodily fluid with a capture binder that binds specifically to ADM-NH_2, preferably an antibody.

12. The use according to any one of claims 1 to 11, wherein the sample of bodily fluid in which of DPP3 is determined or the sample of bodily fluid in which of ADM-NH_2 is determined is selected from blood, serum, plasma, urine, cerebrospinal fluid (CSF), and saliva, preferably plasma.

13. The use according to any one of claims 1 to 12, wherein the anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold binds to the N-terminal part (amino acid 1-10) of ADM: YRQSMNNFQG (SEQ ID No. 26), and wherein preferably said anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold recognizes and binds to the N-terminal end (amino acid 1) of ADM-Gly and/ or ADM-NH_2, and wherein preferably said antibody, antibody fragment or non-Ig scaffold does not bind to the C-terminal portion of ADM, having the sequence amino acid 43-52 of ADM: PRSKISPQGY-NH_2 (SEQ ID NO: 24).

14. The use according to any one of claims 1 to 13, wherein said antibody or fragment or scaffold blocks the bioactivity of ADM not more than 80 %, preferably not more than 50%.

15. The use according to any one of claims 1 to 14, wherein said antibody or fragment is a monoclonal antibody or fragment that binds to ADM or an antibody fragment thereof, wherein the heavy chain comprises the sequences:

CDR1: SEQ ID NO: 1

GYTFSRYW

CDR2: SEQ ID NO: 2

ILPGSGST

CDR3: SEQ ID NO: 3

TEGYEYDGFDY

and wherein the light chain comprises the sequences:

CDR1: SEQ ID NO: 4

QSIVYSNGNTY

CDR2:

RVS

CDR3: SEQ ID NO: 5

FQGSHIPYT.

16. The use according to any one of claims 1 to 15, wherein said antibody or fragment comprises a sequence comprising as a VH region:

SEQ ID NO: 6 (AM-VH-C)

QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGST
NYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTTLTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

SEQ ID NO: 7 (AM-VH1)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

SEQ ID NO: 8 (AM-VH2-E40)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

SEQ ID NO: 9 (AM-VH3-T26-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

SEQ ID NO: 10 (AM-VH4-T26-E40-E55)

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

and comprises a sequence comprising as a VL region:

SEQ ID NO: 11 (AM-VL-C)

DVLLSQTPLSLPVSLGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVSNRF
SGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 12 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSNRD
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 13 (AM-VL2-E40)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSNRD
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

17. The use according to any one of claims 1 to 16, wherein said antibody or fragment comprises the following sequence as a heavy chain:

SEQ ID NO: 32

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWIGEILPGSGST
NYNQKFQGRVTITADTSTSTAYMELSSLRSEDTAVYYCTEGYEYDGFDYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

or a sequence that is > 95% identical to it,
and comprises the following sequence as a light chain:

SEQ ID NO: 33

DVVLTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWYLQRPGQSPRLLIYRVSNRFS
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

or a sequence that is > 95% identical to it.

18. The use according to any of claims 1 to 17, wherein said antibody or fragment or scaffold exhibits a binding affinity to ADM of at least 10^{-7} M by label-free surface plasmon resonance using a Biacore 2000 system.

19. The use according to claim 18, wherein the anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold exhibits an affinity towards human ADM is between 1 x 10^{-9} to 3 x 10^{-9} by label-free surface plasmon resonance using a Biacore 2000 system.

20. The use according to any one of claims 1 to 19, wherein the anti-ADM antibody or anti-ADM antibody fragment is an IgG1 antibody.

21. The use according to any one of claims 1-20, wherein the medicament is provided in a pharmaceutical formulation.

22. The use according to claim 21, wherein said pharmaceutical formulation is a solution, preferably a ready-to-use solution.

23. The use according to claim 121or 22, wherein said pharmaceutical formulation is in a freeze-dried state.

24. The use according to any one of claims 21 to 23, wherein said pharmaceutical formulation is to be administered intra-muscularly.

25. The use according to any one of claims 21 to 24, wherein said pharmaceutical formulation is to be administered intra-vascularly.

26. The use according to any one of claims 21 to 25, wherein said pharmaceutical formulation is to be administered via infusion.

27. The use according to any one of claims 21 to 26, wherein said pharmaceutical formulation is to be administered systemically.