

Claims

1. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in 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. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient 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. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claim 1 and 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. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to 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, more preferred between 30 and 80 ng/mL, even more preferred between 40 and 60 ng/mL, most preferred said threshold is 50 ng/mL.

5. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient 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. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 5, wherein the bodily fluid is selected from whole blood, plasma and serum.
7. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claim 6, wherein the bodily fluid is plasma.
8. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 7, wherein the level of DPP3 is determined by contacting said sample of bodily fluid with a capture binder that binds specifically to DPP3.
9. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claim 8, wherein the capture binder is an antibody.
10. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in the treatment or prevention of shock in a patient according to claims 1 to 9, wherein either the level of DPP3 protein and/or the level of active DPP3 is determined and compared to a predetermined threshold.
11. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 10, wherein said patient is additionally characterized by having a level of ADM-NH₂ above a threshold.

12. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 11, wherein said threshold of ADM-NH₂ in a sample of bodily fluid of said patient is between 40 and 100 pg/mL, more preferred between 50 and 90 pg/mL, even more preferred between 60 and 80 pg/mL, most preferred said threshold is 70 pg/mL.
13. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claim 12, wherein said threshold of ADM-NH₂ in a sample of bodily fluid of said patient is 70 pg/mL.
14. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 13, wherein the bodily fluid is selected from whole blood, plasma and serum.
15. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claim 14, wherein the bodily fluid is plasma.
16. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 11-15, wherein the level of ADM-NH₂ is determined by contacting said sample of bodily fluid with a capture binder that binds specifically to ADM-NH₂.
17. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claim 16, wherein the capture binder is an antibody.
18. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 17, wherein the sample of bodily fluid of said patient is selected from the group of blood, serum, plasma, urine, cerebrospinal fluid (CSF), and saliva.
19. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 18, wherein 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-NH₂.

20. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 19, wherein 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-NH₂ (SEQ ID NO: 24).
21. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 20, wherein said antibody or fragment or scaffold blocks the bioactivity of ADM not more than 80 %, preferably not more than 50%.
22. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 21, 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

TEGYEYDGFYD

and wherein the light chain comprises the sequences:

CDR1: SEQ ID NO: 4

QSIVYSNGNTY

CDR2:

RVS

CDR3: SEQ ID NO: 5

FQGSHIPYT.

23. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 22, wherein said antibody or fragment comprises a sequence selected from the group comprising as a VH region:

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

QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGST
NYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFQDYWGQGTTTLTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

SEQ ID NO: 7 (AM-VH1)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFQDYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFQDYWGQGTTVT

VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFQYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEILPGSGS
TNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCTEGYEYDGFQYWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

and comprises a sequence selected from the group comprising the following sequence as a VL
region:

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

DVLLSQTPSLPVS LGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVSNRF
SGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 12 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSNRD
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSV

FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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

DVVMQTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWVFQQRPGQSPRRLIYRVSNRD
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

24. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1 to 23, wherein said antibody or fragment comprises the following sequence as a heavy chain:

SEQ ID NO: 32

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGGLEWIGEILPGSGST
NYNQKFQGRVTITADTSTSTAYMELSSLRSEDVAVYYCTEGYEYDGFQDYWGQGT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYS
KLTVDKSRWQQGNVFSVMHEALHNHYTQKSLSLSPGK

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

SEQ ID NO: 33

DVVLVTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWYLQRPQGQSPRLLIYRVSNRFS
GVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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

25. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 1-24, wherein the anti-adrenomedullin (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).
26. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of claim 25, 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.
27. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claim 26, wherein the anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold exhibits an affinity towards human ADM is between 1×10^{-9} to 3×10^{-9} by label-free surface plasmon resonance using a Biacore 2000 system.
28. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy or prevention of shock in a patient according to claims 25 to 27, wherein the anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold is an IgG1 antibody.
29. Pharmaceutical formulation for use in therapy or prevention of shock of a patient comprising an anti-adrenomedullin (ADM) antibody or an anti-ADM antibody fragment or anti-ADM non-Ig scaffold according to any of claims 1 -28.
30. Pharmaceutical formulation for use in therapy or prevention of shock of a patient according to claim 29, wherein said pharmaceutical formulation is a solution, preferably a ready-to-use solution.
31. Pharmaceutical formulation for use in therapy or prevention of shock of a patient according to claims 29 and 30, wherein said pharmaceutical formulation is in a freeze-dried state.

32. Pharmaceutical formulation for use in therapy or prevention of shock of a patient according to claims 29 and 31, wherein said pharmaceutical formulation is administered intra-muscular.
33. Pharmaceutical formulation for use in therapy or prevention of shock of a patient according to claims 29 and 32, wherein said pharmaceutical formulation is administered intra-vascular.
34. Pharmaceutical formulation for use in therapy or prevention of shock of a patient according to claims 29 and 33, wherein said pharmaceutical formulation is administered via infusion.
35. Pharmaceutical formulation for use in therapy or prevention of shock of a patient according to claims 29 and 34, wherein said pharmaceutical formulation is to be administered systemically.