

Claims

1. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a patient with shock, in particular septic shock, wherein said patient :
 - has suffered from shock, in particular from a septic shock not longer than 10 hours at the starting point of treatment with said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold and/or
 - has been admitted to ICU not longer than 10 hours at the starting point of treatment with said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold, and/or
 - has not received organ support at all or not longer than 10 hours of organ support at the starting point of treatment with said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold, andwherein said antibody or fragment or scaffold binds to the N-terminal part (aa 1-21) of ADM: YRQSMNNFQGLRSFGCRFGTC (SEQ ID No. 4).
2. Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy according to claim 1, wherein said patient has suffered from shock, in particular from a septic shock, not longer than 9, preferably 8.4, preferably 8.26 (0.344days), preferably 8, preferably 7, preferably 6, preferably 5.76 (0.25 days), preferably 5.75 (0.24 days), 5. preferably 4, preferably 3 hours at the starting point of treatment with said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold.
3. Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy according to any of claim 1 to 2, wherein said patient has been admitted to ICU not longer than 9, preferably 8.4, preferably 8.26 (0.344days), preferably 8, preferably 7, preferably 6, preferably 5.76 (0.25 days), preferably 5.75 (0.24 days) preferably 5. preferably 4, preferably 3 hours at the starting point of treatment with said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold.

4. Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy according to any of claim 1 to 3, wherein said patient has received organ support not longer than 9, preferably 8.4, preferably 8.26 (0.344days), preferably 8, preferably 7, preferably 6, preferably 5.76 (0.25 days), preferably 5.75 (0.24 days), preferably 5, preferably 4, preferably 3 hours at the starting point of treatment with said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold
5. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a patient suffering from shock, in particular septic shock, wherein said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold is administered
 - within 10 hours after occurrence of shock in said patient and/or
 - within 10 hours after admission of said patient to ICU, and/or
 - before the patient has received organ support or within not longer than 10 hours of organ support, andwherein said antibody or fragment or scaffold binds to the N-terminal part (aa 1-21) of ADM: YRQSMNNFQGLRSFGCRFGTC (SEQ ID No. 4).
6. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a patient suffering from shock, in particular septic shock according to claim 5 wherein said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold is administered within 9, preferably 8.4, preferably 8.26 (0.344days), preferably 8, preferably 7, preferably 6, preferably 5.76 (0.25 days), preferably 5.75 (0.25 days), preferably 5, preferably 4, preferably 3 hours after occurrence of shock in said patient
7. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a patient suffering from shock, in particular septic shock according to claim 5 or 6, wherein said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold is administered within 9, preferably 8.4, preferably 8.26 (0.344days), preferably 8, preferably 7, preferably 6, preferably 5.76 (0.25 days), preferably 5.75 (0.25 days), preferably 5, preferably 4, preferably 3 hours after admission of said patient to ICU.

8. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a patient suffering from shock, in particular septic shock according to claim 5, 6 or 7, wherein said anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold is administered within 9, preferably 8.4, preferably 8.26 (0.344days), preferably 8, preferably 7, preferably 6, preferably 5.76 (0.25 days), preferably 5.75 (0.25 days), preferably 5, preferably 4, preferably 3 hours after the patient has received organ support at the starting point of treatment with said Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold.
9. Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy according to any of claims 1 to 8, wherein said patient has shock that is selected from the group comprising shock due to hypovolemia, cardiogenic shock, obstructive shock and distributive shock, in particular cardiogenic shock, septic shock, shock due to Covid-19, shock due to burns and traumatic shock.
10. Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy according to claim 9, wherein said patient has septic shock.
11. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a patient suffering from shock, in particular septic shock, according to any of claims 1 to 10, wherein a sample of bodily fluid taken said patient exhibits a level of bioADM > 70 pg/mL, and wherein said bodily fluid is selected from the group comprising whole blood, plasma or serum.
12. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy of a patient suffering from shock, in particular septic shock according to any of claims 1 to 11, wherein a sample of bodily fluid taken said patient exhibits a level of DPP3 < 50 ng/mL, and wherein said bodily fluid is selected from the group comprising whole blood, plasma or serum.

13. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any one of claims 1 to 12, wherein said antibody or antibody fragment or non-Ig scaffold is monospecific.
14. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of claims 1 to 13, 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.
15. Anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to claim 14, wherein antibody or fragment or scaffold exhibits a binding affinity to ADM exhibits a binding affinity to ADM of between 1×10^{-9} to 3×10^{-9} by label-free surface plasmon resonance using a Biacore 2000 system.
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 any one of claims 13 to 15, wherein the anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold is an IgG1 antibody.
17. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of claims 1 to 16, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1 (complement factor H).
18. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of the preceding claims, wherein said antibody or fragment or scaffold recognizes and binds to the N-terminal end (aa 1) of ADM.
19. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of the preceding claims, wherein said antibody or fragment or scaffold is an ADM stabilizing antibody or fragment or scaffold that enhances the half-life ($t_{1/2}$ half retention time) of ADM in serum, blood,

plasma at least 10 %, preferably at least, 50 %, more preferably > 50 %, most preferably > 100 %.

20. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of the preceding claims, wherein said antibody or fragment or scaffold blocks the bioactivity of ADM not more than 80 %, preferably not more than 50% using hADM 22-52 as a reference antagonist in CHO-K1 cells expressing human recombinant ADM receptor.
21. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of the preceding items, wherein said subjects undergoes chemotherapy, vasopressors, treatment with biologics, antibiotics, or treatment with anti-viral compounds.
22. Anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment or anti-ADM non-Ig scaffold for use in therapy according to any of the preceding items, wherein said antibody or fragment is a human monoclonal antibody or fragment that binds to ADM or an antibody fragment thereof wherein the heavy chain comprises the sequences:

CDR1: SEQ ID NO: 5

GYTFSRYW

CDR2: SEQ ID NO: 6

ILPGSGST

CDR3: SEQ ID NO: 7

TEGYEYDGFY

and wherein the light chain comprises the sequences:

CDR1: SEQ ID NO: 8

QSIVYSNGNTY

CDR2:

RVS

CDR3: SEQ ID NO: 9

FQGSHIPYT.

23. A human monoclonal antibody or fragment that binds to ADM or an antibody fragment thereof for use in therapy according to claim 22, wherein said antibody or fragment comprises a sequence selected from the group comprising as a VH region:

SEQ ID NO: 10 (AM-VH-C)

QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILP
GSGSTNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFD
YWGQGTTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKHHHHHH

SEQ ID NO: 11 (AM-VH1)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPQGGLWGMGRIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYCTEGYEYDGFD
YWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKHHHHHH

SEQ ID NO: 12 (AM-VH2-E40)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPQGGLWGMGRIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYCTEGYEYDGFD
YWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKHHHHHH

SEQ ID NO: 13 (AM-VH3-T26-E55)

QVQLVQSGAEVKKPGSSVKV SCKATGYTFSRYWISWVRQAPGQGLEWMGEIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCTEGYEYDGF D
YWGQGT TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKHHHHHHH

SEQ ID NO: 14 (AM-VH4-T26-E40-E55)

QVQLVQSGAEVKKPGSSVKV SCKATGYTFSRYWIEWVRQAPGQGLEWMGEIL
PGSGSTNYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCTEGYEYDGF D
YWGQGT TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKHHHHHHH

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

SEQ ID NO: 15 (AM-VL-C)

DVLLSQTPSLPVS LGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYR
VSNRFSGV PDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGG TKLE
IKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSK DSTYLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
C

SEQ ID NO: 16 (AM-VL1)

DVVM TQSPLSLPVT LGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYR
VSNRDSGV PDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGG TKL
EIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSK DSTYLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC

SEQ ID NO: 17 (AM-VL2-E40)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYR
VSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKL
EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSSTLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRG
EC.

24. A human monoclonal antibody or fragment that binds to ADM or an antibody fragment thereof for use in therapy according to claim 22 or 23, wherein said antibody or fragment comprises the following sequence as a heavy chain:

SEQ ID NO: 22

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWIGEILPG
SGSTNYNQKFQGRVTITADTSTSTAYMELSSLRSEDVAVYYCTEGYEYDGFYDW
QGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHY
TQKSLSLSPGK

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

and comprises the following sequence as a light chain:

SEQ ID NO: 23

DVVLTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWYLQRPQGSPRLLIYRVS
NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGKLEIKR

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV
TEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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. 25).
26. Pharmaceutical formulation for use in therapy or prevention of symptoms of illness or for the use in therapy according to any of claims 1 to 25.