

CLAIMS

1. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock, the method comprising:

- 5 • determining the level of dipeptidyl peptidase 3 (DPP3) in a sample of bodily fluid of said patient, and
- comparing said level of determined DPP3 to a pre-determined threshold,
- wherein a level of DPP3 in said sample below the pre-determined threshold is indicative that treatment with an anti-ADM antibody or anti-ADM antibody fragment
- 10 or anti-ADM non-Ig scaffold is required, and

wherein 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), and wherein the shock is selected from septic shock, cardiogenic shock, distributive shock, hypovolemic shock and

15 obstructive shock.

2. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 1, wherein said shock is cardiogenic shock or septic shock.

3. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 1 or 2, wherein

- 25 • 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
- 30 • 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, or
- 35 • 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. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 3, wherein said pre-determined threshold of DPP3 level in a sample of bodily fluid of said subject 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. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 4, wherein either a level of DPP3 protein and/or a level of active DPP3 is determined and compared to a pre-determined threshold.
6. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock 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.
7. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 6, wherein said determination comprises the use of a capture-binder that binds specifically to full-length DPP3 wherein said capture-binder may be selected from the group of antibody, antibody fragment or non-IgG scaffold.
8. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 7, wherein an amount of DPP3 protein and/or DPP3 activity is determined in a bodily fluid sample of said subject and wherein said determination comprises the use of a capture-binder that binds specifically to full-length DPP3 wherein said capture-binder is an antibody.
9. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 8, wherein an amount of DPP3 protein and/or DPP3 activity is determined in a bodily fluid sample of said subject and wherein said determination comprises the use of a capture-binder that binds specifically to full-length DPP3 wherein said capture-binder is immobilized on a surface.

10. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 9, wherein the amount of DPP3 protein and/or DPP3 activity is determined in a bodily fluid sample of said subject and wherein said separation step is further comprising a washing step that removes ingredients of the sample that are not bound to said capture-binder from the captured DPP3.

11. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 10, wherein determining DPP3 activity in a bodily fluid sample of said subject comprises the steps:

- contacting said sample with a capture-binder that binds specifically to full-length DPP3,
- separating DPP3 bound to said capture binder,
- adding substrate of DPP3 to said separated DPP3,
- quantifying of said DPP3 activity by measuring and quantifying the conversion of a substrate of DPP3.

12. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 11, wherein DPP3 activity is determined in a bodily fluid sample of said subject and wherein DPP3 substrate conversion is detected by a method selected from the group consisting of: fluorescence of fluorogenic substrates (e.g. Arg-Arg- β NA, Arg-Arg-AMC), color change of chromogenic substrates, luminescence of substrates coupled to aminoluciferin (Promega Protease-Glo™ Assay), mass spectrometry, HPLC/ FPLC (reversed phase chromatography, size exclusion chromatography), thin layer chromatography, capillary zone electrophoresis, gel electrophoresis followed by activity staining (immobilized, active DPP3) or western blot (cleavage products).

13. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 11, wherein DPP3 activity is determined in a bodily fluid sample of said subject and wherein said substrate may be selected from the group consisting of: angiotensin II, III and IV, Leu-enkephalin, Met-enkephalin, endomorphin 1 and 2, valorphin, β -casomorphin, dynorphin, proctolin, ACTH and MSH, or di-peptides coupled to a fluorophore, a chromophore or aminoluciferin wherein the di-peptide is Arg-Arg.

14. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 11, wherein DPP3 activity is determined in a bodily fluid sample of said subject and wherein said substrate may be

selected from the group consisting of: A di-peptide coupled to a fluorophore, a chromophore or aminoluciferin wherein the di-peptide is Arg-Arg.

- 5 15. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 14, wherein said patient is additionally characterized by having a level of ADM-NH₂ above a threshold.
- 10 16. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 15 wherein said threshold of ADM-NH₂ in a sample of bodily fluid of said patient is between 40 and 100 pg/mL, or between 50 and 90 pg/mL, or between 60 and 80 pg/mL, or is 70 pg/mL.
- 15 17. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 15 or 16, 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.
- 20 18. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 17, wherein the sample of bodily fluid of said patient is selected from the group consisting of blood, serum, plasma, urine, cerebrospinal fluid (CSF), and saliva.
- 25 19. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 15 to 17, wherein the level of DPP3 and the level of ADM-NH₂ is determined in combination.
- 30 20. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 19, wherein the level of DPP3 and the level of ADM-NH₂ is determined simultaneously.
- 35 21. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 19 or 20, wherein the level of DPP3 and the level of ADM-NH₂ is determined using a point-of-care device.

22. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to claim 21, wherein said point-of-care device is a microfluidic device.

5 23. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 22, 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.

10 24. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 23, 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).

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25. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 24, 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:

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CDR1: SEQ ID NO: 1

GYTFSRYW

CDR2: SEQ ID NO: 2

25

ILPGSGST

CDR3: SEQ ID

NO: 3

TEGYEYDGF

30

Y

and wherein the light chain comprises the sequences:

CDR1: SEQ ID

NO: 4

QSIVYSNGN

5 Y

CDR2:

RVS

10 CDR3: SEQ ID NO: 5

FQGSHIPYT.

26. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 25, wherein said antibody or fragment comprises a sequence comprising as a VH region:

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

QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGSTNY
NEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFQDYWGQGTTTLTVSSAS
20 TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

SEQ ID NO: 7 (AM-VH1)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYCTEGYEYDGFQDYWGQGTTTVTVSSA
25 STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

QVQLVQSGAEVKKPGSSVKVSCASGYTFSRYWIEWVRQAPGQGLEWMGRILPGSGSTN
 YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTEGYEYDGFQYWGQGTTVTVSSA
 STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
 YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

5

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

QVQLVQSGAEVKKPGSSVKVSCATGYTFSRYWISWVRQAPGQGLEWMGEILPGSGSTN
 YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTEGYEYDGFQYWGQGTTVTVSSA
 STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
 YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

10

or

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

QVQLVQSGAEVKKPGSSVKVSCATGYTFSRYWIEWVRQAPGQGLEWMGEILPGSGSTN
 YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTEGYEYDGFQYWGQGTTVTVSSA
 STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
 YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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and comprises a sequence comprising as a VL region:

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

DVLLSQTPSLPVS LGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVS NRFSG
 VPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVFIFPP
 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLT
 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

25

SEQ ID NO: 12 (AM-VL1)

DVVMQTQSPLSPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVS NRDSG
 VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLT
 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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or

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

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

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27. A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient with shock and/ or in a patient running into shock according to any one of claims 1 to 25, wherein said antibody or fragment comprises the following sequence as a heavy chain:

10 SEQ ID NO: 32

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWIGEILPGSGSTNY
NQKFQGRVTITADTSTSTAYMELSSLRSEDTAVYYCTEGYEYDGFQYWGQGTITVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL
15 FPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK

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

SEQ ID NO: 33

DVVLTSQPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWYLQRPGQSPRLLIYRVSNRFSG
25 VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

or a sequence that is > 95% identical to it

30

wherein the heavy chain comprises the sequences:

CDR1: SEQ ID NO: 1

GYTFSRYW

CDR2: SEQ ID NO: 2

ILPGSGST

5 CDR3: SEQ ID NO: 3

TEGYEYDGFDY

and wherein the light chain comprises the sequences:

10 CDR1: SEQ ID NO: 4

QSIVYSNGNTY

CDR2:

RVS

15

CDR3: SEQ ID NO: 5

FQGSHIPYT.