

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,
- comparing said level of determined DPP3 to a pre-determined threshold, and
- and wherein the level of DPP3 in said sample is indicative of whether a treatment with an anti-ADM antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold
- 10 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).
- 15 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, the method comprising:
- determining the level of dipeptidyl peptidase 3 (DPP3) in a sample of bodily fluid of said patient,
- 20 • comparing said level of determined DPP3 to a pre-determined threshold, and
- administering an anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold to said patient, wherein said patient is treated with said anti-adrenomedullin (ADM) antibody or anti-ADM antibody fragment or anti-ADM non-Ig scaffold if said determined level of DPP3 is below a pre-determined
- 25 threshold, 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).
- 30 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 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.

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 according to claims 1 to 3, 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, 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.
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 claims 1 to 4, wherein said pre-determined threshold of DPP3 level in a sample of bodily fluid of said subject 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.
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 claims 1 to 5, wherein either the level of DPP3 protein and/or the level of active DPP3 is determined and compared to a pre-determined threshold.
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 claims 1 to 6, wherein the level of DPP3 is determined by contacting said sample of bodily fluid with a capture binder that binds specifically to DPP3.
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 claim 1 to 7, 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.

- 5 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 claims 1 to 8, wherein the 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.
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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 claims 1 to 9, wherein the 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.
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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 claims 1 to 10, 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 a washing step that removes ingredients of the sample that are not bound to said capture-binder from the captured DPP3.
- 20
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 claims 1 to 11, wherein the method for determining DPP3 activity in a bodily fluid sample of said subject comprises the steps:
- 25
- 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,
 - 30 • quantifying of said DPP3 activity by measuring and quantifying the conversion of a substrate of DPP3.
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 claims 1 to 12, wherein the 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 comprising: fluorescence of fluorogenic substrates (e.g. Arg-Arg-βNA, Arg-Arg-AMC), color change of chromogenic
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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).

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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 claims 1 to 13, wherein the DPP3 activity is determined in a bodily fluid sample of said subject and wherein said substrate may be selected from the group comprising: 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.
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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 claims 1 to 14, wherein the DPP3 activity is determined in a bodily fluid sample of said subject and wherein said substrate may be selected from the group comprising: A di-peptide coupled to a fluorophore, a chromophore or aminoluciferin wherein the di-peptide is Arg-Arg.
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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 claims 1 to 15, wherein said patient is additionally characterized by having a level of ADM-NH₂ above a threshold.
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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 16 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.
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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 claims 16 and 17, 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.
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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 claims 1 to 18, wherein
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the sample of bodily fluid of said patient is selected from the group of blood, serum, plasma, urine, cerebrospinal fluid (CSF), and saliva.

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 claims 1 to 19, wherein the level of DPP3 and the level of ADM-NH₂ is determined in combination.
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 20, wherein the level of DPP3 and the level of ADM-NH₂ is determined simultaneously.
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 claims 20 and 21, wherein the level of DPP3 and the level of ADM-NH₂ is determined using a point-of-care device.
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 claim 22, wherein said point-of-care device is a microfluidic device.
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 claims 1 to 23, 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.
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 claims 1 to 24, 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).
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 claims 1 to 25, 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
- GYTFSTRYW

CDR2: SEQ ID NO: 2

ILPGSGST

5 CDR3: SEQ ID NO: 3

TEGYEYDGFY

and wherein the light chain comprises the sequences:

10 CDR1: SEQ ID NO: 4

QSIVYSNGNTY

CDR2:

RVS

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CDR3: SEQ ID NO: 5

FQGSHIPYT.

20 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 claims 1 to 26, wherein said antibody or fragment comprises a sequence selected from the group comprising as a VH region:

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

25 QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPBGHGLEWIGEILPGSGSTNY
NEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFYWGQGTTLTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEK

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SEQ ID NO: 7 (AM-VH1)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWISWVRQAPGQGLEWMGRILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTEGYEYDGFQYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
5 YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWMGRILPGSGSTN
YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTEGYEYDGFQYWGQGTTVTVSSA
10 STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWISWVRQAPGQGLEWMGEILPGSGSTN
15 YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTEGYEYDGFQYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

QVQLVQSGAEVKKPGSSVKVSCKATGYTFSRYWIEWVRQAPGQGLEWMGEILPGSGSTN
20 YAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCTEGYEYDGFQYWGQGTTVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK

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

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

DVLLSQTPSLPVS LGDQATISCRSSQSIVYSNGNTYLEWYLQKPGQSPKLLIYRVSNRFSG
30 VPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHIPYTFGGGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLT
LSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

SEQ ID NO: 12 (AM-VL1)

DVVMQTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVIYCFQGSHPYTFGQGTKLEIKRTVAAPSVFIFPP
5 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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

DVVMQTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSNRDSG
10 VPDRFSGSGSGTDFTLKISRVEAEDVGVIYCFQGSHPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

28.A method for therapy guidance and/ or therapy monitoring and/ or therapy stratification in a patient
15 with shock and/ or in a patient running into shock according to claims 1 to 26, wherein said
antibody or fragment comprises the following sequence as a heavy chain:

SEQ ID NO: 32

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSRYWIEWVRQAPGQGLEWIGEILPGSGSTNY
20 NQKFQGRVTITADTSTSTAYMELSSLRSEDVAVYYCTEGYEYDGFYWGQGTITVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVTVPPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
25 QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHREALHNHYTQKSLSLSPGK

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

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SEQ ID NO: 33

DVVLQTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWYLQRPQGSPRLLIYRVSNRFSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVIYCFQGSHPYTFGGGTKLEIKRTVAAPSVFIFPP

SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

or a sequence that is > 95% identical to it

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wherein the heavy chain comprises the sequences:

CDR1: SEQ ID NO: 1

GYTFSRYW

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CDR2: SEQ ID NO: 2

ILPGSGST

CDR3: SEQ ID NO: 3

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TEGYEYDGFY

and wherein the light chain comprises the sequences:

CDR1: SEQ ID NO: 4

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QSIVYSNGNTY

CDR2:

RVS

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CDR3: SEQ ID NO: 5

FQGSHIPYT.