al.; Mapping of the Adrenomedullin-Binding domains in Human Complement factor H; Hypertens Res Vol. 26, Suppl (2003), S56-59).

In accordance with the invention the ADM-binding-Protein-1 may be also referred to as ADM-binding-Protein-1 (complement factor H).

Patients having a chronic or acute disease or acute condition may be in need for stabilizing the circulation or their hemodynamic function (Cavazonni and Dellinger, Critical Care 2006, 10(Suppl 3):S2 (doi:10.1186/cc4829).

Summary

In one aspect, there is provided the use of anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient for stabilizing the systemic circulation of said patient.

In another aspect, there is provided the Use of a pharmaceutical formulation comprising an anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient as disclosed herein.

Description of the invention

Subject matter of the present invention is an anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to ADM for use in therapy of an acute disease or acute condition of a patient for stabilizing the circulation, in particular the systemic circulation of said patient. In particular, subject matter of the present invention is an anti-adrenomedullin (ADM) antibody or an anti-adrenomedullin antibody fragment binding to ADM or anti-ADM non-Ig scaffold binding to ADM for use in therapy of an acute disease or acute condition of a patient for stabilizing the systemic circulation of said patient wherein said patient is in need of stabilizing the circulation.

Systemic circulation refers to the part of the circulatory system in which the blood leaves the heart, services the body's cells, and then re-enters the heart. Blood leaves through the left ventricle to the aorta, the body's largest artery. The aorta leads to smaller arteries, arterioles, and

finally capillaries. Waste and carbon dioxide diffuse out of the cell into the blood, and oxygen in the blood diffuses into the cell. Blood then moves to venous capillaries, and then to the venae cavae: the lower inferior vena cava and the upper superior vena cava, through which the blood re-enters the heart at the right atrium.

Throughout the specification stabilizing the circulation means stabilizing the systemic circulation. The term systemic circulation would not encompass phenomena of microcirculation. Microcirculation is the delivery of fresh blood to the smallest blood vessels, present in the vasculature embedded within organ tissues. This contrasts with macrocirculation, which transport blood to and from the organs. The state of the systemic circulation may be measures by parameters like mean arterial pressure, blood pressure (other

CLAIMS

1. Use of ~~A~~anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin ~~for use~~ in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient for stabilizing the systemic circulation of said patient.

2. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin~~ The use according to claim 1,

   a) ~~for use in therapy of an acute disease or acute condition of a patient for stabilizing the systemic circulation of said patient~~ wherein said patient is in need of stabilizing the systemic circulation and exhibits a heart rate of > 100 beats /min and/ or < 65 mm Hg mean arterial pressure and wherein stabilizing the systemic circulation means increasing the mean arterial pressure over 65 mmHg; or

   b) ~~for preventive use in therapy of an acute disease or acute condition of a patient in order to~~ wherein the medicament prevents ~~that~~ the heart rate from increasinges to > 100 beats /min and/ or mean arterial pressure from decreasinges to < 65 mm Hg.

3. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 1 or 2, wherein said antibody or fragment or scaffold reduces the vasopressor requirement, *e.g.* catecholamine requirement of said patient.

4. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 3, wherein said antibody or antibody fragment or non-Ig scaffold is a non-neutralizing anti-ADM antibody or a non-neutralizing anti-adrenomedullin antibody fragment or a non-neutralizing anti-ADM non-Ig scaffold.

5. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 4, wherein said antibody or antibody fragment or non-Ig scaffold is monospecific.

6. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 5, wherein said antibody or fragment or scaffold exhibits a binding affinity to ADM of at least 10^{-7} M.

7. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 6, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1 (complement factor H).

8. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 7, wherein said antibody or antibody fragment or non-Ig scaffold binds to a region of preferably at least 4, or at least 5 amino acids within the sequence of aa 1-42 of mature human ADM:

YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA
(SEQ ID NO: 24).

9. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 8, wherein said antibody or fragment or scaffold binds to a region of preferably at least 4, or at least 5 amino acids within the sequence of aa 1-21 of mature human ADM:

YRQSMNNFQGLRSFGCRFGTC
(SEQ ID NO: 23).

10. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 9, wherein said antibody or fragment or scaffold recognizes and binds to an epitope containing the N-terminal end amino acid 1 of mature human ADM and wherein said antibody or fragment or scaffold would neither bind N-terminal extended nor N-terminal modified adrenomedullin nor N-terminal degraded adrenomedullin.

11. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or ani-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 10, wherein said antibody or fragment or scaffold is an ADM stabilizing antibody or fragment or scaffold that enhances the half life (t1/2 half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, or at least 50 %, or > 50 %, or >100 %.

12. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 11, wherein said antibody or fragment or scaffold blocks the circulating ADM bioactivity not more than 80 %, preferably not more than 50%.

13. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 12, wherein said antibody or fragment or scaffold is a modulating anti-ADM antibody or a modulating anti-adrenomedullin antibody fragment or modulating anti-ADM non-Ig scaffold that enhances the half life (t1/2 half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, or at least 50 %, or > 50 %, or >100 % and that blocks the bioactivity of ADM to not more than 80 %, preferably not more than 50 %.

14. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of claims 1 to 13, 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

SEQ ID NO: 1
GYTFSRYW

SEQ ID NO: 2
ILPGSGST

SEQ ID NO: 3
TEGYEYDGFDY

and wherein the light chain comprises the sequences
SEQ ID NO:4
QSIVYSNGNTY

SEQ ID NO: 5
RVS

SEQ ID NO: 6
FQGSHIPYT.

15. ~~An anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 14, wherein said antibody or fragment comprises the sequences:

SEQ ID NO: 7 (AM-VH-C)
QVQLQQSGAELMKPGASVKISCKATGYTFSRYWIEWVKQRPGHGLEWIGEILPGSGS
TNYNEKFKGKATITADTSSNTAYMQLSSLTSEDSAVYYCTEGYEYDGFDYWGQGTT
LTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS

SEQ ID NO: 14 (AM-VL2-E40)
DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSN
RDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

16. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the claims 1 to 15, wherein said disease is selected from the group comprising SIRS, sepsis, diabetes, cancer, acute vascular diseases as *e.g.* heart failure, shock as *e.g.* septic shock and organ dysfunction as *e.g.* kidney dysfunction.

17. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the claims 1 to 16, characterized in that said antibody, antibody fragment or non-Ig scaffold does not bind to the C-terminal portion of ADM, being it aa 43-52 of ADM (SEQ ID NO: 25)
PRSKISPQGY-NH2
(SEQ ID NO: 25).

18. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the claims 1 to 17, wherein the medicament is to be used in combination with catecholamine and/ or fluids administered intravenously.

19. ~~Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the

claims 1 to ~~17 or a combination according to claim~~ 18, wherein the medicament is to be used in combination with ADM binding protein and/or further active ingredients.

20. Use of a ~~P~~pharmaceutical formulation comprising an anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin ~~for use~~ in the manufacture of a medicament for therapy of an acute disease or acute condition of a patient according to any of claims 1 to 19.

21. ~~Pharmaceutical formulation for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 20, wherein said pharmaceutical formulation is a solution, or a ready-to-use solution.

22. ~~Pharmaceutical formulation for use in therapy of an acute disease or acute condition of a patient~~ The use according to claim 21, wherein said pharmaceutical formulation is in a freeze-dried state.

23. ~~Pharmaceutical formulation comprising an anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig scaffold binding to adrenomedullin for use in therapy of an acute disease or acute condition of a patient~~ The use according to any of the claims 21 to 23, wherein said pharmaceutical formulation is to be administered to a patient for stabilizing the systemic circulation with the proviso that said patient is in need for stabilizing the systemic circulation.