another embodiment, the use of the AQGV peptide, or a functional analogue thereof, is for use in human patients being on a cardiopulmonary bypass pump.

Without being bound by theory, the effect of the AQGV peptide, or a functional analogue thereof, may have an effect on vasoconstriction. Vasoconstriction involves the narrowing of the blood vessels resulting from contraction of the muscular wall of the vessel. Hence, in one embodiment, the use of an AQGV peptide, or a functional analogue thereof, in accordance with the invention, involves inducing vasoconstriction. In particular, the use of AQGV, or an analogue thereof, may induce peripheral vasoconstriction and/or vasoconstriction in efferent arterioles of the kidney. Peripheral vasoconstriction may improve hemodynamics, whereas vasoconstriction in efferent arterioles may improve kidney function.

SUMMARY

In one aspect, the present disclosure refers to use of a peptide in the manufacture of a medicament for treatment of a human subject considered in need of maintaining or improving hemodynamic stability, said peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

In one aspect, the present disclosure refers to use of a peptide in the manufacture of a medicament for treatment of a human subject considered in need of reducing adverse vascular permeability, said peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

In one aspect, the present disclosure refers to use of a peptide in the manufacture of a medicament for treatment of a human subject considered in need of reducing adverse fluid, said peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

In one aspect, the present disclosure refers to a pharmaceutical formulation comprising a peptide as defined above, and at least one pharmaceutically acceptable excipient.

In one aspect, the present disclosure refers to a stock solution comprising a pharmaceutical formulation as defined above.

In one aspect, the present disclosure refers to use of a pharmaceutical formulation or solution as defined above in the manufacture of a medicament for treatment of a human subject considered in need of maintaining or improving hemodynamic stability.

In one aspect, the present disclosure refers to use of a pharmaceutical formulation or solution as defined above in the manufacture of a medicament for treatment of a human subject considered in need of reducing adverse vascular permeability.

In one aspect, the present disclosure refers to use of a pharmaceutical formulation or solution as defined above in the manufacture of a medicament for treatment of a human subject considered in need of reducing adverse fluid retention.

In one aspect, the present disclosure refers to use of a pharmaceutical formulation or solution as defined above in the manufacture of a medicament for treatment of a human subject suffering or considered suffering from Clarkson's disease (CLS).

FIGURE LEGENDS

FIG. 1. An overview of the timeline with procedures of the EASI-study (JMIR Res. Protol. 2019 Feb 6;8(2):e11441. doi: 10.2196/11441) from inclusion until end of follow-up. The EASI-study is a prospective, randomized, double-blind, placebo-controlled study in which 180 elective patients undergoing on-pump coronary artery bypass grafting (CABG) with or without concomitant valve surgery were enrolled. Patients were randomized in a 1:1 ratio to receive either EA-230, 90 mg/kg/hour, or placebo, infused from the start of the surgical procedure until the end of the use of the cardiopulmonary bypass (CBP). 89 patients received placebo, 91 patients received EA-230, administered i.v. via 2-4 hour continuous i.v. infusion.

FIG. 2. Depicted is the need for vasopressors in the first 24 hours of intensive care unit (ICU) after the surgery. In the total group (FIG. on top) and related to treatment duration. As study drug infusion was continued as long as the patient was on cardiopulmonary bypass, treatment duration was variable (figures below). Modulation in vasopressor use during the first 24 hours of ICU admission were determined and expressed as the composite inotropic score: (dopamine dose × 1 μg/kg/min) + (dobutamine dose × 1 μg/kg/min) + (adrenaline dose × 100 μg/kg/min) + (noradrenaline dose × 100 μg/kg/min) + (phenylephrine dose × 100 μg/kg/min) + (vasopressin (mUnits/kg/min)*10000) + (milrinone x10 mcg/kg/min) (Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2010 Mar; 11(2):234-8. PMID: 19794327. doi:

CLAIMS

~~1. A method of treatment of a human subject considered in need of maintaining or improving hemodynamic stability comprising administering to said subject a peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).~~

~~2. A method of treatment of a human subject considered in need of reducing adverse vascular permeability comprising administering to said subject a peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).~~

~~3. A method of treatment of a human subject considered in need of reducing adverse fluid retention comprising administering to said subject a peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).~~

~~4. A method of treatment according to anyone of claims 1-3 wherein said peptide comprises at least 75% amino acids selected from said group of autophagy inhibiting amino acids.~~

~~5. A method of treatment according to anyone of claims 1-4 wherein said peptide consists of amino acids selected from said group of autophagy inhibiting amino acids.~~

~~6. A method of treatment according to anyone of claims 1-5 wherein said peptide comprises at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (A), glutamine (Q), and leucine (L).~~

~~7. A method of treatment according to anyone of claims 1-6 wherein said peptide comprises at most 30% amino acids selected from the group of autophagy inhibiting amino acids glycine (G), valine (V), isoleucine (I), proline (P) and arginine (R).~~

~~8. A method of treatment according to anyone of claims 1-7 comprising administering to said subject at least two different peptides each comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).~~

~~9. A method according to anyone of claims 1-8 wherein said peptide or peptides vary in length from 4-30 amino acids.~~

~~10. A method of treatment according to anyone of claims 1-9 wherein said subject has been subjected to severe trauma such as surgery.~~

~~11. A method of treatment according to anyone of claims 1-9 wherein said subject has been subjected to cancer treatment such as treatment with an antineoplastic or immunomodulating agent.~~

~~12. A method of treatment according to anyone of claims 1-9 wherein said subject is considered to suffer from capillary leakage syndrome such as seen with an adverse drug reaction.~~

~~13. A method according to anyone of claims 1-12, the human subject having impaired kidney function.~~

~~14. A method according to anyone of claims 1-13, wherein the method comprises a reduced use of vasopressive agents.~~

~~15. A method according to anyone of claims 1-14, wherein the method comprises a reduced fluid intake.~~

~~16. A method according to anyone of claims 1-15 wherein the peptide comprises at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G) and valine (V).~~

~~17. A method according to anyone of claims 1-15 wherein the peptide consists of amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G) and valine (V).~~

~~18. A method according to anyone of claims 1-17 wherein the peptide is a salt selected from the group of peptide-organic acid.~~

~~19.~~1. Use of a~~A~~ peptide in the manufacture of a medicament for ~~use in~~ treatment of a human subject considered in need of maintaining or improving hemodynamic

stability, said peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

~~20.~~2. Use of a~~A~~ peptide in the manufacture of a medicament for ~~use in~~ treatment of a human subject considered in need of reducing adverse vascular permeability, said peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

~~21.~~3. Use of a~~A~~ peptide in the manufacture of a medicament for ~~use in~~ treatment of a human subject considered in need of reducing adverse fluid, said peptide comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

~~22.~~4. ~~A~~The ~~peptide~~ use according to any one of claims ~~19-21~~ 1-3, wherein said subject has been subjected to severe trauma, such as surgery, to cancer treatment, such as treatment with an antineoplastic or immunomodulating agent, or wherein said subject is considered to suffer from capillary leakage syndrome, such as seen with an adverse drug reaction.

~~23. A peptide according to anyone of claims 19-21 wherein said subject has been subjected to cancer treatment such as treatment with an antineoplastic or immunomodulating agent.~~

~~24. A peptide according to anyone of claims 19-21 wherein said subject is considered to suffer from capillary leakage syndrome such as seen with an adverse drug reaction.~~

~~25.~~5. ~~A~~ The ~~peptide~~ use according to any one of claims ~~19-24~~ 1-4, wherein the human subject ~~having~~ has impaired kidney function.

~~26.~~6. ~~A~~ The ~~peptide~~ use according to any one of claims ~~19-25~~ 1-5, wherein the use further comprises a reduced use of vasopressive agents and/or a reduced fluid intake.

~~27. A peptide according to anyone of claims 19-26, wherein the use comprises a reduced fluid intake.~~

~~28.~~7. ~~A~~ The ~~peptide~~ use according to any one of claims ~~19-27~~ 1-6, wherein the peptide comprises at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G) and valine (V), preferably wherein the peptide consists of amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G) and valine (V).

~~29. A peptide according to claim 28 wherein the peptide consists of amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G) and valine (V).~~

~~30.~~8. ~~A~~ The ~~peptide~~ use according to claim ~~29~~ 7, wherein the peptide is a salt selected from the group of peptide-acetate, peptide-tartrate or peptide-citrate.

~~31.~~9. A pharmaceutical formulation comprising a peptide ~~according to anyone~~as defined in any one of claims ~~19-30~~1-8, and at least one pharmaceutically acceptable excipient.

~~32.~~10. ~~A~~ The pharmaceutical formulation according to claim ~~31~~ 9, wherein said peptide comprises at least 75% amino acids selected from said group of autophagy inhibiting amino acids, preferably wherein said peptide consists of 100% amino acids selected from said group of autophagy inhibiting amino acids.

~~33. A pharmaceutical formulation according to anyone of claims 31 or 32 wherein said peptide consists of 100% amino acids selected from said group of autophagy inhibiting amino acids.~~

~~34.~~11. ~~A~~ The pharmaceutical formulation according to ~~anyone of claims 31-33~~claim 9 or 10, wherein said peptide comprises at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (A), glutamine (Q), and leucine (L).

~~35.~~12. ~~A~~ The pharmaceutical formulation according to any one of claims ~~31-34~~9-11, wherein said peptide comprises at most 30% amino acids selected from the group of autophagy inhibiting amino acids glycine (G), valine (V), isoleucine (I), proline (P) and arginine (R).

~~36.~~13. ~~A~~ The pharmaceutical formulation according to any one of claims ~~31-35~~9-12, comprising at least two different peptides each comprising at least 50% amino acids selected from the group of autophagy inhibiting amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

~~37.~~14. ~~A~~ The pharmaceutical formulation according to any one of claims ~~31-36~~9-13, wherein said peptide or peptides vary in length from 4-30 amino acids.

~~38.~~15. ~~A~~ The pharmaceutical formulation to any one of claims ~~31-37~~9-14, comprising at least 0.85mol/L of said peptide or peptides.

~~39. A pharmaceutical formulation according to anyone of claims 31-38 and at least one pharmaceutically acceptable excipient.~~

~~40.~~16. A stock solution comprising a pharmaceutical formulation according to any one of claims ~~31-39~~9-15.

~~41.~~17. Use of a~~A~~ pharmaceutical formulation or solution according to any one of claims ~~31-40~~9-16 in the manufacture of a medicament for ~~use in a method of~~ treatment of a human subject considered in need of maintaining or improving hemodynamic stability.

~~42.~~18. Use of a~~A~~ pharmaceutical formulation or solution according to any one of claims ~~31-40~~9-16 in the manufacture of a medicament for ~~use in a method of~~ treatment of a human subject considered in need of reducing adverse vascular permeability.

~~43.~~19. Use of a~~A~~ pharmaceutical formulation or solution according to any one of claims ~~31-40~~9-16 in the manufacture of a medicament for ~~use in a method of~~ treatment of a human subject considered in need of reducing adverse fluid retention.

~~44.~~20. Use of a~~A~~ pharmaceutical formulation or solution according to any one of claims ~~31-40~~9-16 in the manufacture of a medicament for ~~use in a method of~~ treatment of a human subject suffering or considered suffering from Clarkson's disease (CLS).

~~45. A method of treatment of a human subject considered in need of maintaining or improving hemodynamic stability comprising administering to said subject a formulation or solution according to anyone of claims 31-40.~~

~~46. A method of treatment of a human subject considered in need of reducing adverse vascular permeability comprising administering to said subject a formulation or solution according to anyone of claims 31-40.~~

~~47. A method of treatment of a human subject considered in need of reducing adverse fluid retention comprising administering to said subject a formulation or solution according to anyone of claims 31-40.~~

~~48. A method of treatment of a human subject suffering or considered suffering from Clarkson's disease (CLS) comprising administering to said subject a formulation or solution according to anyone of claims 31-40.~~