BRIEF SUMMARY ~~OF THE INVENTION~~

In one aspect, the present disclosure refers to use of a substance in the manufacture of a medicament for reducing the permeability of an endothelial layer of a blood vessel in a subject, wherein the substance is to be provided to the endothelial layer and reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection. In one aspect, the present disclosure also refers to a pharmaceutical formulation for any one of the uses disclosed herein.

In a first ~~embodiment~~example, the ~~invention~~disclosure provides a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, such as with a virus. In a preferred ~~embodiment~~example, the ~~invention~~disclosure provides said method for reducing the gas diffusion distance between lung-alveoli and the vascular network surrounding alveoli in a human subject suffering from a respiratory infection, allowing reduction of fluid in alveoli and/or allowing improved oxygen supply to the subject's body. In a preferred ~~embodiment~~example, said substance comprises an AQGV-peptide, an LQGV-peptide, or a functional analogue of either. In a preferred ~~embodiment~~example, the ~~invention~~disclosure provides said method for reducing the gas diffusion distance between lung-alveoli and the vascular network surrounding alveoli in a human subject suffering from an infection with a respiratory virus. It is moreover preferred that said viral infection is caused by a virus requiring a specific receptor and a more ubiquitous binding partner present on at least a percentage of lung alveolar cells. In one preferred ~~embodiment~~example, it is preferred that said specific receptor is ACE-2. In another preferred ~~embodiment~~example, it is preferred that the more ubiquitous binding partner is a glycoprotein comprising a sialic acid residue. It is in particular preferred that said ubiquitous binding partner binds with a fMLF-like amino acid sequence, for example wherein said sequence at least comprises a membrane-proximal-external-region (MPER, herein also identified as fusogenic sequence). It is in particular preferred that said virus is a coronavirus, in particular a coronavirus with an MPER as identified in figure 11, more in particular at least comprising a fusogenic sequence as identified in figure 12. It is most preferred that said MPER at least comprises amino acid sequence KWPWIWL (amino acids identified herein by one-letter code). In a further preferred ~~embodiment~~example, the ~~invention~~disclosure provides a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, such as with a virus, wherein the coronavirus is the COVID-19 virus (SARS-COV-2) or a mutant thereof.

The ~~invention~~disclosure also provides a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, wherein said substance is administered intravenously to said subject, preferably at a rate of at least 75mg/kg/hr, or more preferably at least 90 mg/kg/hr. It is moreover preferred that the substance is administered intermittently. It is moreover preferred that during treatment the subject is monitored for haemodynamic stability. The ~~invention~~disclosure also provides a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, wherein said substance is administered intravenously to said subject, said method further comprising administering an antiviral agent, such as remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase, to the subject. The ~~invention~~disclosure also provides a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, wherein said substance is administered intravenously to said subject, said method further comprising administering an anti-inflammatory agent, such as dexamethasone or an interleukin-6 signaling inhibitors such as tocilizumab, to the subject.

The ~~invention~~disclosure also provides a pharmaceutical formulation for use in a method for reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, wherein said substance is administered intravenously to said subject, preferably at a rate of at least 75mg/kg/hr, or more preferably at least 90 mg/kg/hr. It is moreover preferred that the substance is administered intermittently. It is moreover preferred that during treatment the subject is monitored for haemodynamic stability. The ~~invention~~disclosure also provides a pharmaceutical formulation for use in reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of

Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, wherein said substance is administered intravenously to said subject, said method further comprising administering an antiviral agent, such as remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase, to the subject. The ~~invention~~disclosure also provides a pharmaceutical formulation for use in reducing the permeability of an endothelial layer of a blood vessel in a subject, the method comprising providing to the endothelial layer a substance that reduces the ratio of Angiopoietin-2 to Angiopoietin-1 at the site of increased permeability as a result of an infection, wherein said substance is administered intravenously to said subject, said method further comprising administering an anti-inflammatory agent, such as dexamethasone or an interleukin-6 signaling inhibitors such as tocilizumab, to the subject.

The ~~invention~~disclosure also provides a pharmaceutical formulation for use according to the ~~invention~~disclosure, comprising an AQGV-peptide, an LQGV-peptide, or a functional analogue of either and an excipient suitable for parenteral administration.

When a human subject is suffering from an infection, in particular a viral infection, more in particular a viral respiratory infection, many effects are seen that influence hemodynamic stability. One of the effects seen is increased permeability of blood vessels leading to fluid leakage from blood vessels into the intercellular spaces, and vice versa, resulting in aggravated and traumatic damage to the lung, and other organs. Typical signs of such suffocating damage induced by leakage from vessels include increased extra-cellular fluid in lungs with fluid overflow into alveoli. Also, thrombosis may be seen, in particular leading to (deep) venous thrombosis ((D)VT) and pulmonary embolism (PE). Particularly in respiratory infections, this all may lead to an increased diffusion distance for gasses such as oxygen and carbon dioxide to traverse the distance between alveoli and blood, and to hypoxemia. Oxygen and carbon dioxide both need to pass through a thin layer in the lungs called the alveolar-capillary membrane. This is the thin layer between the small air sacks in the lung (the alveoli) and the smallest blood vessels that travel through the lungs (lung-capillaries). How well oxygen is inhaled and can pass (diffuse) from the alveoli into the blood, and how well carbon dioxide can pass from the blood capillaries back into the alveoli to be exhaled, depends on how thick (swollen) this membrane is, and how much surface area is available for the transfer to take place.

This problem is aggravated in people already suffering from limited oxygen availability through underlying disease. Diffusing capacity may be low if there is less surface area available for the transfer of oxygen and carbon dioxide, for example with emphysema, or if a lung or part of it is removed for lung cancer, or PE and or pre-existing cardiovascular and metabolic issues and obesity.

Also, diffusing capacity may be low if lung disease is present that causes the membrane to be thicker, for example in chronic lung disease such as pulmonary fibrosis, as for example seen with COPD, and with sarcoidosis. The present ~~invention~~disclosure is particularly useful for such patients having only partial lung capacity.

Acute disease can also result in low diffusing capacity, for example in aggravated viral respiratory infections with injury to the lung, often the permeability of lung-capillaries is increased generating a flux of fluid from the capillaries into the thin layer of extra-cellular-matrix separating alveoli from capillaries, with intercellular fluid retention therewith thickening (swelling) the membrane through accumulation of fluid in the extra-cellular-matrix (interstitium) separating alveolar cells from vascular cells. In such lung injury patients and patients with aggravated infectious airway infections, plasma levels of biomarkers of endothelial activation, as may be measured by ELISA, are often predictive of mortality and morbidity. In particular, the concentration of angiopoietin-2 relative to angiopoietin-1 (Ang-2/Ang-1) may be a useful biologic marker of mortality in acute lung injury (ALI) patients. Ang-2/Ang-1 is found significantly higher in patients who died of lung injury [p=0.01; Crit Care Med. 2010 Sep; 38(9): 1845–1851.]. In a multivariable analysis stratified by dead space fraction, Ang-2/Ang-1 was an independent predictor of death with an adjusted odds ratio of 4.3 (95% CI 1.3–13.5, p=0.01) in those with an elevated pulmonary dead space fraction (p=0.03 for interaction between pulmonary dead space fraction and Ang-2/Ang-1).

Similarly, D-dimer plasma levels may be used to follow a patient's health status in aggravated viral respiratory infections with injury to the lung and endothelial activation. D-dimer, the lysis product of cross-linked fibrin indicates fibrinolysis in response to clotting activation and fibrin formation (doi.org/10.1111/jth.12075). D-dimer levels are evident in febrile and convalescent phases typically following viral infections that affect vascular endothelial cells and associate with endothelial activation and plasma leakage. D-dimer assays can vary in sensitivity depending on the

lab-specific type drawn, and not all labs report the same units providing various acceptable ranges for the results. There are many things that can cause elevated D-dimer beyond venous thromboembolism (VTE), such as age or pregnancy. The D-dimer half-life of 8 hours results in elevated levels for approximately 3 days after the inciting event. Quantitative D-dimer holds a sensitivity of 94% to 98%, yet only specificity of 50% to 60%. This allows to utilize it as a screening tool but requires clinical evidence from the history and physical examination, preferably with intermittent repeated testing to confirm the diagnosis or follow a patient's health status.

Thus, the ~~invention~~disclosure in one aspect provides a method for reducing the permeability of an endothelial layer of a blood vessel comprising providing to the layer a substance reducing the ratio of angiopoietin-2 to angiopoietin-1 at the site of increased permeability as a result of an infection.

In one ~~embodiment~~example this method serves to reduce the gas diffusion distance (or at least to prevent increasing the diffusion distance) between lung-alveoli and the vascular network surrounding alveoli in a human subject suffering from a respiratory infection, in particular patients with underlying disease causing limited oxygen availability. Reduced vascular permeability in patients suffering vascular leakage is generally associated with reduced D-dimer levels. According to the ~~invention~~disclosure, in one ~~embodiment~~example the substances to be used in the methods according to the ~~invention~~disclosure include peptides that influence hemodynamics, particularly by influencing gap junctions between the cells. Such peptides include AQGV and functional analogues thereof. A functional analogue is defined as a substance that provides the same or a similar function (in kind, not necessarily in amount). Basically, any substance that decreases permeability of the vascular system may be used according to the present ~~invention~~disclosure. For one, tetrapeptide AQGV (herein also referred to as EA-230) has surprisingly been found to modulate vascular permeability to the good. In particular, EA-230 significantly improves hemodynamic stability in humans, even in the absence of inflammatory activity of the patient. Permeability governs the amount of fluid leaking from blood vessels. Administration of fluid therapy generally increases leakage. Based on Phase II trial patient observations, we found a significant reduction of adverse fluid retention (fluid leakage) in patients treated with EA-230 ($p = 0.03$). Throughout clinical trials, EA-230 was shown to be safe and well tolerated. EA-230 shows significant improvements in patient recovery, over placebo patient. EA-230 treated patients are released faster from intensive care ($p=0.0232$) and hospital ($p=0.0015$).

EA-230 improves hemodynamic stability (p=0.006) and kidney function (p=0.003). Long-term patient recovery was significantly improved by EA-230. By improving vascular permeability, EA-230 can be used to reduce the infection-associated occurrence of adverse fluid in the lungs, reduce hypoxemia, reduce PE, and therewith also reduce ventilator use with its detrimental systemic effects, in particular in viral respiratory infections such as caused by influenza viruses and in particularly by coronaviruses. Thus, provided is in particular a method according to the ~~invention~~disclosure wherein the active substance to control hemodynamic stability comprises an AQGV peptide. A functional and/or structural AQGV analogue according to the ~~invention~~disclosure may be selected from the group consisting of peptides comprising a tetrapeptide selected from the group of AQLP, PLQA, LQGV, LAGV, PQVG, PQVA, PQVR, VGQL, LQPL, RQGV, LQVG, LQGA, LQGR, AQGA, QPLA, PQVP, VGQA, QVGQ, VGQG or other permutations of peptides of 4-12 amino acids constituted of particularly the amino acids of the above tetrapeptides. The ~~invention~~disclosure further provides a method wherein the viral infection is caused by a virus requiring a specific receptor and a more ubiquitous binding partner present on at least a percentage of lung alveolar cells. In one preferred ~~embodiment~~example, the viral infection is caused by a coronavirus wherein the specific receptor is ACE-2, in particular wherein the coronavirus is SARS-Cov-2 or a mutant or analogue thereof. Other coronavirus infections which may be treated according to the ~~invention~~disclosure carry specific receptor DPP4 (such as with MERS corona virus) or APN (aminopeptidase N). Also preferred is a method wherein the more ubiquitous binding partner is a glycoprotein comprising a sialic acid residue. It is in particular preferred that said ubiquitous binding partner binds with a fMLF-like amino acid sequence, for example wherein said sequence at least comprises a membrane-proximal-external-region (MPER, herein also identified as fusogenic sequence). Such a method according to the ~~invention~~disclosure is in particular provided wherein the virus is a coronavirus. It is in particular preferred that said virus is a coronavirus, in particular a coronavirus with an MPER as identified in figure 11, more in particular at least comprising a fusogenic sequence as identified in figure 12. Alternatively, the more ubiquitous binding partner is a glycoprotein comprising a sialic acid residue as recognized by influenza virus. The combination of a specific and a more ubiquitous binding/infection site on a cell is typical for coronaviruses, with their typical effect on the hemodynamics as disclosed herein. In a further preferred ~~embodiment~~example, provided is a method wherein the AQGV peptide or related

substance is administered intravenously, preferably at a rate of at least 75mg/kg/hr., more preferably at least 90 mg/kg/hr. It is in particular useful to administer the AQGV peptide or related substance intermittently. Preferred use is dosing for 2-4 hours at at least 90mg/kg/hour, then reducing to 30mg/kg/hour for 2-4 hours, or for as long as it takes to monitor the patients response to treatment by clinical or laboratory diagnosis, or stop administering the substance for 1-2 hours until diagnostic studies such as point-of-care testing have completed, and then resume treatment with 2-4 hours at at least 90mg/kg/hour. It is preferred that the monitoring comprises studying the subject for hemodynamic stability and/or fibrinolysis. Treatment with AQGV peptide according to the ~~invention~~disclosure may further comprise administering an antiviral agent. The ~~invention~~disclosure also provides a pharmaceutical formulation comprising an AQGV peptide or related substance (preferably a functional analogue) for use in a method according to the ~~invention~~disclosure, or a pharmaceutical formulation for use according to the ~~invention~~disclosure, comprising an AQGV peptide, or a functional analogue thereof and an excipient suitable for parenteral administration.

Often, the human subject or patient experiencing reduced diffusion, may be admitted into an intensive care unit (ICU) where vital signs are monitored. The patient receives medical treatment to allow the patient to recover and when vital signs are within acceptable boundaries, the patient can be released from ICU and admitted into standard hospital care. When the patient has shown to be stable at standard care, the patient can be released from the hospital and returns home. Subsequently, a patient can be readmitted into the hospital should the need arise because e.g. the condition or infection status of the patient worsens. Any improvement on the health and recovery of a patient affecting the length of stay of a patient in the ICU, the length of stay in standard care at the hospital and/or patient re-admittance, provides for a significant benefit to patients. Hence, any means and methods according to the ~~invention~~disclosure that improve the health and in particular speed of recovery of a patient through use of the peptide compounds disclosed herein are of interest.

Upon testing in a clinical trial aimed at assessing the safety and tolerability of an AQGV peptide (also referred to as EA-230 herein) and its immunomodulatory effects, the peptide was found to be safe but, unexpectedly, no immunomodulatory effects were observed under the test circumstances when comparing treated patients as compared with control subjects. Instead of

observing immunomodulatory effects, the current inventors surprisingly found that upon analysis of the data obtained in the clinical trial, new and highly advantageous properties could be attributed to the AQGV peptide, which have not been observed before. These properties are apparently independent from known and observed immunomodulatory effects.

Hence, the current ~~invention~~disclosure relates to the use of an AQGV peptide, and analogues thereof, for improving the clinical parameters of human patients admitted into hospital and/or intensive care such that the time period between admittance and release from hospital and/or intensive care can be shortened. In one ~~embodiment~~example, the use of an AQGV peptide, and analogues thereof, is for use in a medical treatment for modifying hemodynamics in human subjects. In a further ~~embodiment~~example, the use in human subjects for modifying hemodynamics, involves a reduction of reducing undesired fluid retention and/or a reduced use of vasopressive agents in the human subject. In another ~~embodiment~~example, the use of an AQGV peptide, and analogues thereof, is for use in human subjects having impaired lung function.

In one ~~embodiment~~example, an AQGV peptide, or a functional analogue thereof, is provided for use in a method of treatment of a human subject, wherein the use comprises a treatment for modifying hemodynamics in the human subject. Hemodynamics involves the dynamics of blood flow, i.e. the physical factors that govern blood flow through the human body. Hemodynamics in human patients can be monitored by measuring e.g. blood pressure and/or the fluid balance. When blood pressure is low and/or the fluid balance disturbed in a human patient, vasopressors, or inotropes may be used and/or fluid administered, e.g. intravenously. Inotropes and vasopressors are biologically and clinically important vasoactive medications that originate from different pharmacological groups and act at some of the most fundamental receptor and signal transduction systems in the body. More than 20 such agents are in common clinical use, yet few reviews of their pharmacology exist outside of physiology and pharmacology textbooks. Despite widespread use in critically ill patients, understanding of the clinical effects of these drugs in pathological states is poor. Adverse effects of vasopressors and inotropes depend on the mechanism of action. For the medications that have beta stimulation, arrhythmias are one of the most common adverse effects that one would like to reduce.

The current inventors have found that by using an AQGV peptide, or a functional analogue thereof, the hemodynamics in human patients post-trauma (e.g. viral infection) was significantly improved as shown by e.g. a reduced use of vasopressors and/or an improved fluid balance in human patients. The use of an AQGV peptide, or a functional analogue thereof, as described herein thus improves the hemodynamic stability in human patients. Modifying or optimizing hemodynamics in human subjects is of importance post-injury, when e.g. human subjects have suffered infection, trauma and/or blood loss. Hence, the AQGV peptide, or an analogue thereof, can advantageously be used in hemodynamic therapy. Hemodynamic therapy comprises the optimization of hemodynamics in patients in goal-directed hemodynamic therapy. Such therapies can include therapeutic interventions such as fluid management in patients and/or the use of vasopressors.

AQGV functional analogues are defined herein as peptides exerting analogous effect or function as the AQGV peptide as described herein, in kind not necessarily in amount. The AQGV peptide has a length of 4 amino acids. An AQGV functional analogue may have sequence identity, i.e. comprising at least part or the whole of the AQGV peptide. Preferably, such an AQGV functional analogue is a structural analogue of the AQGV peptide. A preferred structural analogue may be an LQGV peptide. Structural analogues of the AQGV peptide may be selected from peptides comprising amino acids selected from the group of amino acids alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), proline (P) and arginine (R). In a preferred ~~embodiment~~example, provided is for a AQGV structural analogue, that comprises at least 50%, more preferably at least 75%, most preferably at least 100% 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), proline (P), and arginine (R). Preferably, a structural analogue of the AQGV peptide has a length in the range of 4-12 amino acids. Preferably, such a structural analogue is a linear peptide. Suitable structural analogues of AQGV may have a length less than 4, e.g. of 3, however such lengths may require higher doses of such peptides because the half-life of such peptides will be shorter and thus less preferred. Longer structural analogues, e.g. longer than 12 residues, are less preferred because of potential immunogenicity of such longer peptides. A structural AQGV analogue according to the ~~invention~~disclosure may be selected from the group consisting of peptides comprising a tetrapeptide

selected from the group of AQLP, PLQA, LQGV, LAGV, PQVG, PQVA, PQVR, VGQL, LQPL, RQGV, LQVG, LQGA, LQGR, AQGA, QPLA, PQVP, VGQA, QVGQ, VGQG.

Vasopressors are a class of drugs that can elevate low blood pressure. Some vasopressors act as vasoconstrictors, other vasopressor sensitize adrenoreceptors to catecholamines - glucocorticoids, and another class of vasopressors can increase cardiac output. Whichever vasopressor is used, the current ~~invention~~disclosure allows for a reduction in the use of vasopressors. A reduction in the use of vasopressors involves a reduction of the duration of vasopressor use and/or a reduction of the dosage of the vasopressor. Examples of vasopressors are e.g. epinephrine, noradrenaline, phenylephrine, dobutamine, dopamine, and vasopressin. Fluid management in patients involves monitoring e.g. oral, enteral, and/or intravenous intake of fluids and fluid output (e.g. urine) and subsequently managing fluid intake e.g. in case of an observed fluid retention (i.e. the fluid intake exceeds fluid output). Strikingly, the use of the AQGV peptide, or an analogue thereof, can reduce fluid retention. Hence, the AQGV peptide, or analogue thereof, can be used in addition to known interventions that are to improve the hemodynamics in human patients, thereby resulting in a faster improvement in hemodynamics as compared with not using an AQGV peptide, or an analogue thereof.

In another ~~embodiment~~example, an AQGV peptide, or a functional analogue thereof, is provided for use in the treatment of a human subject having impaired lung function. In a further ~~embodiment~~example, the impaired lung function is acute lung injury. In one ~~embodiment~~example, an AQGV peptide, or a functional analogue thereof, is provided for use in the treatment of a human subject for improving lung function. Lung function can also be assessed by measuring hypoxemia, or by determining the alveolar–arterial gradient (A-aO2, or A–a gradient). Assessing A-a gradient to assess lung function in humans is standard clinical practice (e.g. by determining the difference between the alveolar concentration (A) of oxygen and the arterial (a) concentration of oxygen. It is used in diagnosing the source and degree of hypoxemia. The A–a gradient helps to assess the integrity of the alveolar capillary unit. Improvements in lung function as compared with not receiving the AQGV peptide can include progressing to a lung function stage to a less severe stage (e.g. a patient progressing from having lung injury to being at risk of lung injury or having no lung injury). Irrespective of what assessment is made, the use of the AQGV peptide, or analogue thereof, can

improve lung function in humans having lung injury and/or an impairment of lung function in subjects absent of immunomodulatory effects.

The use of the AQGV peptide allows for improving lung function, however, it can also prevent a reduction and/or an impairment of lung function. Accordingly, lung injury with hypoxemia may be prevented. Hence, in one ~~embodiment~~example, the use of the AQGV peptide, or analogue thereof, allows to maintain lung function in human patients. Hence, the use of the AGQV peptide, or analogue thereof allows to protect lung function in human patients. In another ~~embodiment~~example, the use of the AQGV peptide, or analogue thereof, allows to prevent a reduction and/or impairment of lung function in human patients. For example, a human patient that can be classified as having no lung injury, or being at risk of having lung injury (such as with COVID-19), may receive treatment with the AQGV peptide, whereby such a patient may maintain its status instead of progressing to a (more severely) reduced lung function. Hence, human patients that are at risk of developing lung injury, e.g. due to (induced) trauma, such as infection, may, as a result of receiving treatment with the AQGV peptide, or analogue thereof, maintain their lung function status.

In another ~~embodiment~~example, an AQGV peptide, or a functional analogue thereof, is provided for use in the treatment of a human subject having impaired lung function whereby the use comprises modifying hemodynamics in the human subject. As treatment of lung function and treatment of hemodynamic stability can now be linked, the use of an AQGV peptide, or a functional analogue thereof, in accordance with the ~~invention~~disclosure can advantageously be used to protect lung function and/or improve lung function, and modifying hemodynamics. Such combined use resulting e.g. in improved and/or maintained lung function and a reduction in the use of vasopressors and/or improved fluid management in human subjects.

In a further ~~embodiment~~example, the current ~~invention~~disclosure provides for a reduced use of vasopressive agents. The use of vasopressive agents can be reduced by reducing the duration of the use of vasopressive agents. The use of vasopressive agents can be reduced by reducing the amount of vasopressive agents (e.g. reducing amount per dosage and/or increasing time interval between administrations). The use of vasopressive agents can be reduced by reducing the amount of vasopressive agents and the duration of the use of vasopressive agents. By reducing the use of

vasopressive agents, human subjects advantageously recover more quickly as compared with human subjects not receiving AQGV, or an analogue thereof.

In another ~~embodiment~~example, the use of an AQGV peptide, or a functional analogue thereof, reduces adverse fluid retention in the human subject. Fluid retention can occur in human subjects, symptoms of which e.g. include weight gain and edema. Fluid retention can be the result of reduced lung function and/or impaired hemodynamics. Hence, because the use of AQGV can affect lung function and/or hemodynamic stability in human subjects, the use of AQGV can affect fluid retention as well. Fluid retention can be the result of leaky capillaries. Hence, the use of AQGV, and analogues thereof, may have an effect on the leakiness (permeability) of capillaries, reducing leakage of plasma from the blood to peripheral tissue and/or organs. Most preferably edema can be reduced and/or avoided by the use of AQGV. Such may also be referred to as adverse fluid retention as it has an adverse effect on the patient. Whichever is the cause of fluid retention, the use of an AQGV peptide, or a functional analogue thereof can improve fluid retention dynamics in human subjects thereby alleviating symptoms associated with fluid retention such as weight gain and edema, which subsequently can reduce the use of diuretics.

In another ~~embodiment~~example, the use of the AQGV peptide, or a functional analogue thereof, in accordance with the ~~invention~~disclosure, is not restricted to patients having lung injury and/or requiring hemodynamic therapy. The use of an AQGV peptide, or a functional analogue thereof, in accordance with the ~~invention~~disclosure, includes the treatment of human patients that are believed to be at risk of having lung injury and/or anticipated to require hemodynamic therapy. Such human patients include patients that are to be admitted, or are expected to be admitted, into intensive care. Hence, the use of the AQGV peptide, or a functional analogue thereof, includes a use for trauma, such as infection, as exemplified e.g. in the examples. The use of the AQGV peptide for trauma, such as infection, may be before, but is typically during and/or after infection. It may be preferred that the use of the AQGV peptide, or an analogue thereof, is during infection with a virus. The use of AQGV peptide as is provided herein is in particular useful in patients subjected to a long duration of mechanical ventilation, i.e. longer than 2.5 hours. Hence, in a further ~~embodiment~~example, the use of the AQGV peptide, or an analogue thereof, is during a mechanical ventilation of longer than 2.5 hours and wherein the AQGV peptide or analogue thereof is

administered during the mechanical ventilation. In another, or further, ~~embodiment~~example, the use of an AQGV peptide, or a functional analogue thereof, for use in accordance with the ~~invention~~disclosure is for use is in a human subject having COVID-19. It is well known that shortening the duration of mechanical ventilation is highly correlated with recovery and prevention of re-admittance of patients.

Preferably, the use of the AQGV peptide, or a functional analogue thereof, in accordance with the ~~invention~~disclosure and as described above, involves the administration of the peptide into the bloodstream. It is understood that administration into the bloodstream comprises e.g. intravenous administration or intra-arterial administration. A constant supply of AQGV peptide, or an analogue thereof, is preferred, e.g. via an infusion wherein the AQGV peptide, or analogue thereof, is comprised in a physiological acceptable solution. Suitable physiological acceptable solutions may comprise physiological salt solutions (e.g. 0.9% NaCl) or any other suitable solution for injection and/or infusion. Such physiological solutions may comprise further compounds (e.g. glucose etc.) that may further benefit the human subject, and may also include other pharmaceutical compounds (e.g. vasopressors).

Preferably, the AQGV peptide is administered at a rate which is at least 50 mg/kg patient weight per hour (mg/kg/hr). Preferably the administration rate is at least 60 mg, at least 70, at least 80 or, most preferably, at least 90 mg/kg/hr. Preferably, the AQGV peptide is administered for at least 1 hour, more preferably at least 1.5 hours, most preferably at least 2 hours. Preferably, the administration of the AQGV peptide is at a rate of at least 70 mg/kg/hr. and administered for at least 1 hour, more preferably at least 1.5 hours, most preferably at least 2 hours. Preferably, the administration is during infection. More preferably, the administration is during essentially the entire duration of disease resulting from infection. Typically treatment will start after determination of a level of severity justifying the treatment. Thus the treatment may typically last from its detection until the absence of detectable infection or sufficient recovery to allow for end of treatment.

As shown in the example section, the mean arterial maximum concentrations (mean Cmax) as determined in vivo in humans for EA-230 in the Phase II clinical trial was 30500 ng/mL, in the range of 12500 to 57500 ng/mL. The mean venous Cmax found was 68400 ng/mL, in the range of 19600 to 113000 ng/mL. Hence, whichever means and methods are used for administration of EA-230 (or

AQGV), preferably, means and methods that allow to obtain an arterial Cmax in the range of 10,000 to 60,000 ng/mL and/or a venous Cmax in the range of 15000 to 120000 ng/ml can be contemplated. Thus, the route of administration may not be necessarily be restricted to intravenous administration, but may include other routes of administration resulting in similar venous and/or arterial Cmax concentrations.

In another ~~embodiment~~example, an AQGV peptide, or a functional analogue thereof, is provided for any use in accordance with the ~~invention~~disclosure as described above, wherein the human subject is admitted to intensive care, and wherein the use improves parameters measured of the human subject, the parameters of the human subject typically those being determined to assess whether the patient needs to remain in intensive care or not. As shown above, parameters that are assessed when a human patient is in intensive care include parameters related to lung function and hemodynamics. In any case, the use of the AQGV peptide, or analogue thereof, is to improve such parameters to thereby reduce the length of stay in the intensive care unit. Not only does the use of the AQGV peptide, or analogue thereof reduce the length of stay in the intensive care, the effect of the use of the AQGV peptide, or analogue thereof, also reduces the length of stay in the hospital and reduces re-admittance into the hospital.

In any case, the use of the AQGV peptide, or a functional analogue thereof has a profound effect on lung function and/or hemodynamics in human subjects thereby advantageously benefiting human subjects when e.g. suffering from induced trauma, e.g. when undergoing mechanical ventilation. Hence, in one ~~embodiment~~example, the use of the AQGV peptide, or a functional analogue thereof, is for use in patients subjected to mechanical ventilation. In another ~~embodiment~~example, the use of the AQGV peptide, or a functional analogue thereof, is for use in human patients experiencing or thought to be experiencing COVID-19 or a similar infection.

The ~~invention~~disclosure relates to a distinct and new class of drugs: autophagy inhibiting compounds that comprise peptides and/or amino acids that target the nutrient sensing system of the mechanistic target of rapamycine, mTOR and inhibit autophagy. Upon testing formyl-peptide related signaling effects of an autophagy inhibiting AQGV peptide the peptide was found to unexpectedly attenuate p38/ p38-MK2-HSP27 and/or PI3K/AKT/mTOR pathways that govern signal cytoskeleton contraction in modulating vascular permeability. Hence, the current ~~invention~~disclosure relates to the use of

an autophagy inhibiting peptide herein also referred to as an AQGV peptide, and analogues (functional equivalents) thereof, for improving vascular permeability.

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~~example, the use of an AQGV peptide, or a functional analogue thereof, in accordance with the ~~invention~~disclosure, involves inducing vasoconstriction.

The ~~invention~~disclosure also provides a method for identifying a peptide capable of reducing p38 MAPK kinase activity, comprising providing cells with a peptide comprising amino acids, said amino acids for at least 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably 100%, amino acids selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R), providing said cells with fMLP and detecting phosphorylation of p38 MAPK in the absence and presence of said peptide at an appropriate time interval, preferably in the order of minutes, most preferably from about half a minute to about 5 minutes e.g. 30 to 600 seconds after provision of fMLP, and comparing the results to determine said peptide's effect on said phosphorylation. Having tested the autophagy inhibiting AQGV peptide, we detect FPR-activation of FPR-expressing cells with prototype FPR-ligand fMLP to cause rapidly induced and significant ($p < 0.05$; p38 from 60 to 600 sec, PKB at 600 sec) changes in phosphorylation status of PKB (also known as AKT) (figure 10a) and p38 MAPK kinases (figure 10c), but not (or not detected) in STAT3, JNK (figure 10b) and P42/p44MAPK/ERK1,2 (figure 10d) kinases.

Therewith the ~~invention~~disclosure also provides a method for identifying a peptide capable of reducing PI3K/AKT/mTOR activity, comprising providing cells with a peptide consisting of amino acids, said amino acids for at least 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably 100%, amino acids selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R), providing said cells with fMLP and detecting phosphorylation of PKB (AKT) in the absence and presence of said peptide at an appropriate time interval, preferably in the order of minutes, most preferably from about half a minute to about 5

minutes, e.g.30 to 600. AQGV peptide effects on p38 MAPK (figure 10c) are already detected at 30 seconds after FPR-stimulation, AQGV peptide effects on PKB(AKT) follow (figure 10a) in a bi-phasic pattern at 300 sec. Both AQGV peptide effects on p38 and PKB-mediated signalling last for the full 600 seconds tested whereas the other kinases tested were not affected throughout. As this acute and specific response to treatment shows specific and rapid effects of autophagy-inhibiting-AQGV peptide on p38 signaling in the context of regulation of the PI3K/AKT/mTOR pathway, said pathway is governing the balance between proteolysis and proteogenesis regulating cytoskeleton changes affecting vascular permeability. Such activities are not detected in STAT3, JNK (figure 10b) and P42/p44MAPK/ERK1,2 (figure 10d) kinases tested with AQGV peptide. It is shown that AQGV peptide reduces p38 MAPK kinase activated changes as well as reduces PI3K/AKT/mTOR activated induced changes in cell cytoskeleton reorganization affecting endothelial cell contraction and adverse vascular permeability.

The ~~invention~~disclosure also provides a method for identifying a peptide capable of reducing PI3K/AKT/mTOR activity, comprising providing cells with a peptide consisting of amino acids, said amino acids for at least 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably 100%, amino acids selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R), providing said cells with fMLP and detecting phosphorylation of PKB (AKT) in the absence and presence of said peptide at an appropriate time interval, preferably in the order of minutes, most preferably from about half a minute to about 5 minutes, e.g.30 to 600 seconds after provision of fMLP, and comparing the results to determine said peptide's effect on said phosphorylation. Identified AQGV peptide is useful and capable of addressing adverse vascular permeability, such as manifested by edema with vascular leakage, adverse leukocyte extravasation and hypotension in human subjects.

The ~~invention~~disclosure also provides a method for identifying a peptide capable of reducing PI3K/AKT/mTOR activity, comprising providing cells with a peptide consisting of amino acids, said amino acids for at least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R), providing said cells with fMLP and detecting phosphorylation of PKB (AKT) in the absence and presence of said

peptide at an appropriate time interval, preferably in the order of minutes, most preferably from about half a minute to about 5 minutes, e.g.30 to 600 seconds after provision of fMLP, and comparing the results to determine said peptide's effect on said phosphorylation. The ~~invention~~disclosure therewith also provides method for identifying a peptide capable of reducing cytoskeleton reorganization, comprising providing cells with a peptide consisting of amino acids, said amino acids for at least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R), and providing said cells with fMLP and detecting phosphorylation of p38 MAPK and/or PKB (AKT) in the absence and presence of said peptide at an appropriate time interval, preferably in the order of minutes, most preferably from about half a minute to about 5 minutes after provision of fMLP, and comparing the results to determine said peptide's effect on said phosphorylation.

Typically, as the ~~invention~~disclosure herein provides a molecular mode-of-action (MoA) of the group of autophagy inhibiting peptides its effects do not necessarily depend on their exact sequence. Instead, their constituent amino acids provide common household, "no-danger or tissue-repair" signals to the nutrient-sensing system of mTOR; leading to inhibition of autophagy and resulting in resolve of disease. These tissue-repair signal molecules change the balance of proteogenesis versus proteolysis in a cell of and lead to resolve of disease in three steps:

Administered peptide or amino acid fragments thereof are for taken up by amino acid transport, PEPT1/2 transport, by common endocytosis, in the case of vascular cells by elastin receptor mediated endocytosis or phagocytosis.

Internalized peptide is hydrolyzed and its amino acids are presented to the nutrient-sensing system of mTOR.

Particular amino acids inhibit autophagy, therewith inhibiting proteolysis and leading to proteogenic resolve and pharmaceutical effect.

Various peptides, either derived from breakdown of peptide hormones or assembled as novel synthetic peptide essentially comprising amino acids selected from the group of autophagy inhibiting amino acids, meeting one or more of the characteristics of the above description have been shown in various animal models in mice or rats to provide potent resolve of excess or adverse – local or systemic- vascular permeability through effects on endothelial cells lining our

vasculature. Several have or are being rationally developed further in various stages of human clinical trials. Exploiting the autophagy inhibiting mechanism involved through future clinical application of these autophagy inhibiting compounds and related peptide drugs provides an exciting novel avenue for the rational treatment of disease. However, with several autophagy inhibiting peptide formulations for intravenous application, peptide solubility difficulties have been experienced that decrease availability of autophagy-inhibiting amino acids, necessitating providing stock solutions of peptide in cumbersome large volumes to avoid aggregation of peptide and loss of pharmaceutical effect.

It is a purpose of this disclosure to provide said autophagy-inhibiting amino acids in a most expedient way to a subject deemed in need thereof. Therewith, the ~~invention~~disclosure provides a tartrate or a citrate of a, preferably recombinant or synthetic, autophagy inhibiting peptide, said peptide having an amino acid sequence comprising at least 50%, more preferably at least 75%, most preferably at 100% amino acids selected from the group of autophagy inhibiting amino acids alanine (A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I) and proline (P). More preferably, the ~~invention~~disclosure provides a stock solution, preferably aqueous, comprising a peptide-tartrate or a peptide citrate of a, preferably recombinant or synthetic, autophagy inhibiting peptide, said peptide having an amino acid sequence comprising at least 50%, more preferably at least 75%, most preferably at 100% amino acids selected from the group of autophagy inhibiting amino acids alanine (A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I) and proline (P).

The ~~invention~~disclosure provides a suitable solution for several autophagy inhibiting peptides to mitigate aggregation of said peptides and identifies tartrate (from tartaric acid, preferably from (+)-tartaric acid) and more preferably citrate (from citric acid) as a suitable counter-ion, pharmaceutical excipient or anion of choice for preparing a salt of an autophagy inhibiting peptide that is a neutral peptide as defined herein above. A variety of salts were screened herein to determine their influence on aggregation of neutral peptide according to the ~~invention~~disclosure, indeed revealing that neutral peptide “salts out” of solution in an anion-specific and concentration-dependent manner. Aggregation points of such salts (the point of concentration below which aggregated peptide-salt tends to resolve) Peptide-sulfate, peptide-maleate, peptide-adenosine monophosphate and

peptide-adenosine in aqueous solution were found to show aggravated aggregation in relation to peptide-acetate aggregation, whereas surprisingly tartrate, and more surprisingly peptide-citrate, showed (strongly) reduced aggregation in aqueous solution in comparison to peptide-acetate.

It is preferred that said autophagy inhibiting peptide-salt according to the ~~invention~~disclosure comprises <25% charged residues selected from the group K, H and R. It is more preferred that said autophagy inhibiting peptide comprises <25% charged residues selected from the group D, K, R, H, and E. It is most preferred that said autophagy inhibiting peptide-salt does not comprise residues selected from the group D, K, R, H, and E. It is furthermore preferred that said solution is an aqueous solution. In a most preferred ~~embodiment~~example, the solution is a so-called stock solution, preferably an aqueous stock solution. A stock solution generally is a concentrated solution of an active substance, herein autophagy inhibiting peptide-salt, that will be diluted to some lower concentration for actual use of said substance, a so-called working solution. Such lower concentration working solutions are for example infusion fluids, e.g. for intravenous or intra-abdominal use to which the peptide is added from the stock solution for administrating therapy to a patient, as often seen in critically ill patients, for example at the intensive care of an hospital or at the battlefield. Under such conditions it is useful, and often considered a requisite, to have the active (peptide) drug available in a small (stock) volume for dilution into the infusion fluid. So-called stock solutions are generally provided and used to save solubilisation and preparation time, conserve materials, reduce storage space, and improve the accuracy with which lower concentrated solutions are prepared to work with. Stock solutions of drugs are often prepared and then provided or stored for imminent intravenous use, for example in critically ill patients. However, due to its by default higher peptide concentration, a stock solution with an autophagy inhibiting peptide invariably runs higher risks on peptide drug aggregation than a final working solution. Stock solutions are generally prepared at a concentration well below an aggregation concentration of the salt in question (e.g. 40-50%) to prevent salt-out events under possibly prolonged storage at various ambient conditions. Risk of peptide aggregation (salting-out) is a phenomenon that the ~~invention~~disclosure provides to avoid or mitigate herein with a stock solution according to the ~~invention~~disclosure. Such stock solutions generally are diluted 10- to 100-fold, or more, to provide a suitable working solution. It is however also an object of the present ~~invention~~disclosure to

provide working solutions of the peptide-salts according to the ~~invention~~disclosure. Particularly because in the application of the peptides of the ~~invention~~disclosure relatively high amounts/concentrations of the peptide salts must be given, it is a prerequisite that the working solutions are far away from salting out points and yet are presented in a relatively small volume. A variety of salts were screened herein to determine their influence on aggregation of neutral peptide, indeed revealing that neutral peptide "salts out" of solution in an anion-specific and concentration-dependent manner. Peptide-sulfate and peptide-maleate were found to show aggravated aggregation in relation to peptide-acetate aggregation, whereas surprisingly tartrate, and even more surprisingly peptide-citrate, showed (strongly) reduced aggregation in comparison to peptide-acetate.

The ~~invention~~disclosure therewith contributes to improved solubility of this distinct and new class of drugs that is emerging: small autophagy inhibiting peptides comprising amino acids that preferentially inhibit autophagy and target the nutrient sensing system of the mechanistic target of rapamycin, mTOR. Typically, peptides are defined as having 50 or less amino acids, for the purpose of this disclosure, proteins are defined as having >50 amino acids. A autophagy inhibiting peptide herein is defined as a linear, branched or circular string of no longer than 50 amino acids that comprises a peptide sequence with at least 50%, more preferably at least 75%, most preferably 100% 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), proline (P), isoleucine (I) and arginine ®.

Molecular mode-of-action (MoA) of this group of peptides does not depend on their exact sequence. Instead, their constituent amino acids provide common household, "no-danger or tissue-repair" signals to the nutrient-sensing system of mTOR; leading to inhibition of autophagy and resulting in resolve of disease

In another ~~embodiment~~example, the ~~invention~~disclosure provides a peptide, preferably a salt of an organic acid, such as a maleate, more preferably an acetate, more preferably a tartrate, most preferably a citrate of a, preferably recombinant or synthetic, autophagy inhibiting peptide, said peptide having an amino acid sequence comprising 50%, more preferably at least 75%, most preferably at 100% amino acids selected from the group of autophagy inhibiting amino acids alanine (A), glutamine (Q), leucine (L), valine (V) glycine (G) and proline (P). More preferably, the ~~invention~~disclosure provides a

stock solution, preferably aqueous, comprising a peptide-tartrate or a peptide citrate of a, preferably recombinant or synthetic, autophagy inhibiting peptide, said peptide having an amino acid sequence comprising at least 50%, more preferably at least 75%, most preferably at 100% amino acids selected from the group of autophagy inhibiting amino acids alanine (A), glutamine (Q), glycine (G), valine (V), leucine (L), and proline (P).

Heeding aggregation risk, a vial with a stock solution of AQGV peptide as defined here above for use in a clinical trial hitherto contained no more than (0.8 mol/L) active substrate in solution.

Based on the current ~~invention~~disclosure such a stock solution of an AQGV-salt of an organic acid, in particular of AQGV peptide-maleate, AQGV peptide-acetate AQGV peptide-tartrate or AQGV peptide-citrate (but not of adenosine or adenosine monophosphate) now is provided having an amino acid sequence comprising at least 50%, more preferably at least 75%, most preferably at 100% amino acids selected from the group of autophagy inhibiting amino acids alanine (A), glutamine (Q), glycine (G), valine (V), leucine (L) and proline (P), to contain at least 0.85 mol/L, more preferably at least 0.9 mol/L, more preferably at least 1 mol/L, more preferably at least 1.2 mol/L, more preferably at least 1.4 mol/L, more preferably at least 1.6 mol/L, most preferably at least 1.8 mol/L, of said AQGV peptide-acetate, AQGV peptide tartrate or AQGV peptide-citrate. In a more preferred ~~embodiment~~example, the ~~invention~~disclosure provides a stock-solution of said AQGV peptide-tartrate or said AQGV peptide-citrate wherein the concentration of said AQGV peptide is in the range of 2 mol/L () to 2.5 mol/L. In a more preferred ~~embodiment~~example, the ~~invention~~disclosure provides a stock-solution of said AQGV-peptide-citrate wherein the concentration of said peptide-citrate is in the range of 2.5 mol/L to 3 mol/L. In a more preferred ~~embodiment~~example, the ~~invention~~disclosure provides a stock-solution of said peptide-citrate wherein the concentration of said peptide-citrate is in the range of 3 mol/L to 3.5 mol/L. In a more preferred ~~embodiment~~example, the ~~invention~~disclosure provides a stock-solution of said peptide-citrate wherein the concentration of said peptide-citrate is in the range of 3.5 mol/L to 4.5 mol/L. In a more preferred ~~embodiment~~example, the ~~invention~~disclosure provides a stock-solution of said peptide-citrate wherein the concentration of said peptide-citrate is in the range of 4.5 mol/L to 5.5 mol/L. In a more preferred ~~embodiment~~example, the ~~invention~~disclosure provides a stock-solution of said peptide-citrate wherein the concentration of said peptide citrate is equal to or larger than 5.5 mol/L. It is preferred that said stock solution is an aqueous solution.

It is preferred that said stock solution is an aqueous solution of autophagy inhibiting amino acids comprising a dipeptide AQ, QQ, LQ, GQ, PQ, VQ, AL, LL, QL, GL, PL, VL, QA, QL, QG, QP, QV, LA, LG, LP, LV, a tripeptide AQG, QQG, LQG, GQG, PQG, VQG, ALG, LLG, QLG, GLG, PLG, VLG, QAG, QLG, QGG, QPG, QVG, LAG, LGG, LPG, LVG or a tetrapeptide AQGV, QQGV, LQGV, GQGV, PQGV, VQGV, ALGV, LLGV, QLGV, GLGV, PLGV, VLGV, QAGV, QLGV, QGGV, QPGV, QVGV, LAGV, LGGV, LPGV, LVGV, or a mixture thereof.

It is preferred that a peptide according to the ~~invention~~disclosure has a peptide sequence with length of 2-40 amino acids, preferably 3-30 amino acids, preferably 4-20 amino acids. It is most preferred that said peptide according to the ~~invention~~disclosure has a peptide sequence that comprises at least 6 amino acids, in particular when at least 4 of those inhibit autophagy. A maximum length of a peptide-tartrate or peptide citrate according to the ~~invention~~disclosure preferably comprises at most 50 amino acids, more preferably at most 40 amino acids, more preferably at most 30 amino acids , more preferably at most 20 amino acids, more preferably at most 15 amino acids, more preferably at most 12 amino acids, most preferably at most 9 amino acids.

The ~~invention~~disclosure provides a method for reducing p38 MAPK kinase activity leading to cytoskeleton reorganization, comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said source is an AQGV peptide as provided herein, said amino acids for least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine ®.

The ~~invention~~disclosure provides a method for reducing formyl-peptide-receptor (FPR) mediated p38 MAPK kinase activity, comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said source is an AQGV peptide as provided herein, said amino acids for least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine ®.

The ~~invention~~disclosure provides a method for reducing PI3K/AKT/mTOR activity leading to cytoskeleton reorganization, comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said

source is an AQGV peptide as provided herein, said amino acids for least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine ®.

The ~~invention~~disclosure provides a method for reducing formyl-peptide-receptor (FPR) mediated PI3K/AKT/mTOR activity, comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said source is an AQGV peptide as provided herein, said amino acids for least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine ®.

The ~~invention~~disclosure provides a method for reducing cytoskeleton reorganization, comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said source is an AQGV peptide as provided herein, said amino acids for least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine ®.

The ~~invention~~disclosure provides a method for reducing formyl-peptide-receptor (FPR) mediated cytoskeleton reorganization, comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said source is an AQGV peptide as provided herein, said amino acids for least 50% selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine ®.

The ~~invention~~disclosure provides a method for modifying vascular permeability comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said source is an AQGV peptide as provided herein, selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine ®.

The ~~invention~~disclosure provides a method for improving tissue repair comprising providing cells, preferably having a formyl-peptide-receptor associated with their surface, with a source of autophagy inhibiting amino acids, preferably wherein said source is an AQGV peptide as provided herein,

selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

The ~~invention~~disclosure provides a method according to the ~~invention~~disclosure, wherein said peptide comprising said autophagy inhibiting amino acids comprises a dipeptide AQ, QQ, LQ, GQ, PQ, VQ, AL, LL, QL, GL, PL, VL, QA, QL, QG, QP, QV, LA, LG, LP, LV, a tripeptide AQG, QQG, LQG, GQG, PQG, VQG, ALG, LLG, QLG, GLG, PLG, VLG, QAG, Q0LG, QGG, QPG, QVG, LAG, LGG, LPG, LVG or a tetrapeptide AQGV, QQGV, LQGV, GQGV, PQGV, VQGV, ALGV, LLGV, QLGV, GLGV, PLGV, VLGV, QAGV, QLGV, QGGV, QPGV, QVGV, LAGV, LGGV, LPGV, LVGV, or a mixture thereof.

In another ~~embodiment~~example, this application finds the SARS-COV-2 spike protein (see also figures 11-13) to carry a distinct peptide-motif sequence KWPWYIWL or variant KWPWYVWL in a membrane proximal external region (MPER) capable of binding to a receptor of the FPR-family of receptors. COVID-19 is activating FPR-mediated pathways, in particular through interaction of vascular cells with its spike protein, therewith leading to vascular leakage, thrombotic events and modulating Ang1/Ang2 ratio. Said MPER region may as well be involved in sparsely reported and incidental thrombotic events after vaccination with distinct coronavirus-based-vaccines that express said spike protein not fixated in a prefusion state. As AQGV-peptide inhibits formyl peptide-activated FPR-mediated pathways (p38-MK2-HSP27 and PI3K-AKT-mTOR, see figure 10) involved in disrupting vascular integrity, AQGV-peptide improves vascular leakage and thrombotic events by inhibiting thrombus formation and modulating Ang1/Ang2 ratio after events causing expression of at least said fusogenic region with motif KWPWYIWL or variant KWPWYVWL in a subject. Surprisingly, said fusogenic region with motif KWPWYIWL or variant KWPWYVWL also comprises an FPR-binding site participating in inducing vascular leakage in a subject. Therewith, the present application also provides alternative treatment or use A method of treatment of a subject deemed to express a peptide or protein comprising a fusogenic region derived from a virus, said method comprising adoptive cell therapy using at least one cell provided with a receptor recognizing said fusogenic site. It is preferred that said fusogenic region at least comprises peptide motif KWPWYIWL or at least comprises peptide motif KWPWYVWL, in particular wherein said cell is a transformed T-cell, such as a CAR-T or TCR-T cell, preferably wherein said cell is directed against a (preferably CD8+) T-cell epitope comprising or overlapping said fusogenic region. Such adoptive

cellular therapy (see for example June et al, Adoptive cellular therapy: A race to the finish line *Science Translational Medicine* 25 Mar 2015: Vol. 7, Issue 280, pp. 280ps7) as here provided uses of at least one cell provided with a receptor recognizing a fusogenic region derived from a virus in method of treatment of a subject deemed to express a peptide or protein comprising said fusogenic region, wherein said fusogenic region at least comprises peptide motif KWPWYIWL or at least comprises peptide motif KWPWYVWL, and wherein said cell is a transformed T-cell, such as a CAR-T or TCR-T cell preferably directed against a (preferably CD8+) T-cell epitope comprising or overlapping said fusogenic region.

FURTHER ~~EMBODIMENT~~EXAMPLES

1. An AQGV peptide, or a functional analogue thereof, for use in the treatment of a human subject, the use comprising modifying hemodynamics in the human subject.
2. An AQGV peptide, or a functional analogue thereof, for use in the treatment of a human subject, wherein the human subject is suffering from a viral infection and wherein the use comprises modifying hemodynamics in the human subject.
3. An AQGV peptide, or a functional analogue thereof, for use in the treatment of a human subject having impaired lung function, the use comprising modifying hemodynamics and improving hypoxemia in the human subject.
4. An AQGV peptide, or a functional analogue thereof, for use as in accordance with any one of further ~~embodiment~~examples 1-3, wherein the use reduces fluid retention in the human subject.
5. An AQGV peptide, or a functional analogue thereof, for use in accordance with any of further ~~embodiment~~examples 1-4 wherein the use comprises a reduced use of vasopressive agents.
6. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~examples 1-5 wherein the use comprises a reduced fluid intake.
7. An AQGV peptide, or a functional analogue thereof, for use in accordance with further ~~embodiment~~example 5, wherein the reduced use of vasopressive agents comprises a reduced duration of vasopressive agent use.
8. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~examples 3-6, wherein the subject is suffering from a respiratory viral infection.

9. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~example 3-8 wherein the use improves lung function in the human subject.

10. An AQGV peptide, or a functional analogue thereof, for use in accordance with further ~~embodiment~~example 9, wherein the improved lung function involves an improved oxygen saturation of blood.

11. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~example 3-10, wherein the human subject has impaired lung function the impaired lung function being ARDS.

12. An AQGV peptide, or a functional analogue thereof, for use as in accordance with any one of further ~~embodiment~~example 1-11, wherein the use reduces leakage of plasma from the blood to peripheral tissue and/or organs.

13. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~example 1-12, wherein the use is in a human subject suffering from or at risk of suffering from detrimental effects of mechanical ventilation.

14. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~example 1-13, wherein the use is in a human subject at risk of having edema.

15. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~example 2-14, wherein the human subject is suffering or thought to be suffering from to corona virus infection.

16. An AQGV peptide, or a functional analogue thereof, for use in accordance with further ~~embodiment~~example 15, wherein the infection is SARS-Cov-2 infection.

17. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~example 1-16, wherein the peptide is administered into the bloodstream.

18. An AQGV peptide, or a functional analogue thereof, for use in accordance with further ~~embodiment~~example 17, wherein the peptide is administered at a rate of at least 70 mg/ kg body weight / hour.

19. An AQGV peptide, a functional analogue thereof, for use in accordance with further ~~embodiment~~example 15 or further ~~embodiment~~example 16, wherein the peptide is administered for at least 1 hour.

20. An AQGV peptide, a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~examples 15-19, wherein the administration is intermittent.

21. An AQGV peptide, or a functional analogue thereof, for use in accordance with any one of further ~~embodiment~~examples 1-20, wherein the human subject is admitted into intensive care, and wherein the use improves parameters measured of the human subject, the parameters of the human subject determined to assess remaining in intensive care.

22. An AQGV peptide, or a functional analogue thereof, for use in accordance with further ~~embodiment~~example 21, wherein the improvement in parameters results in a reduced length of stay at intensive care.

23. An AQGV peptide, or a functional analogue thereof, for use as in accordance with any one of further ~~embodiment~~examples 1-22, wherein the uses induces vasoconstriction.

24. An AQGV peptide, or a functional analogue thereof, for use as in accordance with any one of further ~~embodiment~~examples 1-23, wherein the subject is deemed at risk of VALI or VILI.

25. An AQGV peptide, or a functional analogue thereof, for use as in accordance with any one of further ~~embodiment~~examples 1-23, wherein the subject is deemed to express a peptide or protein comprising a fusogenic region derived from a virus.

26. An AQGV peptide, or a functional analogue thereof, for use as in accordance with further ~~embodiment~~example 25, wherein said fusogenic region at least comprises peptide motif KWPWYIWL or variant KWPWYVWL.

27. An AQGV peptide, or a functional analogue thereof, for use as in accordance with further ~~embodiment~~example 25 or 26 , wherein said fusogenic region at least comprises an FPR-binding site.

28. A method of treatment comprising administering an AQGV peptide, or a functional analogue thereof, to a human subject, the human subject being in need of maintaining hemodynamic stability.

29. A method of treatment comprising administering an AQGV peptide, or a functional analogue thereof, to a human subject, the human subject being in need of improving hemodynamic stability.

30. A method of treatment comprising administering an AQGV peptide, or a functional analogue thereof, to a human subject, the human subject having impaired lung function, wherein

the treatment of administering an AQGV peptide comprises maintaining or improving hemodynamic stability in the human subject.

31. A method of treatment comprising administering an AQGV peptide, or a functional analogue thereof, intermittently to a human subject, the human subject having impaired lung function, wherein the treatment of administering an AQGV peptide comprises maintaining or improving hemodynamic stability in the human subject.

31. A method of treatment of a subject deemed to express a peptide or protein comprising a fusogenic region derived from a virus, said method comprising adoptive cell therapy using at least one cell provided with a receptor recognizing said fusogenic site.

32. A method according to further ~~embodiment~~example 31 wherein said fusogenic region at least comprises peptide motif KWPWYIWL

33. A method according to further ~~embodiment~~example 31 wherein said fusogenic region at least comprises peptide motif KWPWYVWL.

33. A method according to any of further ~~embodiment~~examples 31 to 33 wherein said cell is a transformed T-cell, such as a CAR-T or TCR-T cell.

34. A method according to ~~embodiment~~example 33 wherein said cell is directed against a T-cell epitope comprising or overlapping said fusogenic region.

35. Use of at least one cell provided with a receptor recognizing a fusogenic region derived from a virus in method of treatment of a subject deemed to express a peptide or protein comprising said fusogenic region.

36. Use according to further ~~embodiment~~example 35 wherein said fusogenic region at least comprises peptide motif KWPWYIWL

37. Use according to further ~~embodiment~~example 35 wherein said fusogenic region at least comprises peptide motif KWPWYVWL.

38. Use according to any of further ~~embodiment~~examples 35 to 37 wherein said cell is a transformed T-cell, such as a CAR-T or TCR-T cell.

39. Use according to ~~embodiment~~example 38 wherein said cell is directed against T-cell epitope comprising or overlapping said fusogenic region.