

effects of the peptide on systemic inflammation (SIRS) during experimental human endotoxemia. At t = 0 hours, 2 ng/kg E. Coli endotoxin was administered i.v. followed by a 2-hour continuous i.v. infusion of tetrapeptide with SEQ ID NO: 2 (AQGV) or placebo. Levels of circulating cytokines and adhesion molecules as well as body temperature and flu-like symptoms were assessed.

The tetrapeptide with SEQ ID NO: 2 (AQGV) was well tolerated and showed an excellent safety profile. Treatment with at 180mg/kg (the highest dose) of the peptide, but not with the lower doses tested, resulted in a significant attenuation of the endotoxin induced increase in plasma levels of IL-6, IL-8, IL-1RA, MCP-1, MIP-1 α , and MIP-1 β and the adhesion molecule VCAM-1. Furthermore, the highest dose reduced fever and flu-like symptoms. It was concluded that administration of the tetrapeptide with SEQ ID NO: 2 (AQGV) is safe and results in attenuation of the systemic inflammatory response in humans. However, a drawback of the here above discussed di-, tri- and tetra-peptides for parenteral application is that they run the chance of being rapidly hydrolyzed in the blood before they have reached their target cells and can exert their beneficial actions. This rapid loss of peptide necessitates using high doses and long applications times to obtain the desired beneficial effects.

Summary

In one aspect, the present disclosure refers to use of a molecule specifically recognizing an elastin receptor complex in the manufacture of a medicament for lowering autophagy comprising targeting cells having said complex associated with their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).

In one aspect, the present disclosure refers to use of a molecule specifically recognizing an elastin receptor complex in the manufacture of a medicament for modifying vascular permeability comprising targeting cells having said complex associated with their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).

In one aspect, the present disclosure refers to use of a molecule specifically recognizing an elastin receptor complex in the manufacture of a medicament for improving tissue repair comprising targeting cells having said complex associated with their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).

5 In one aspect, the present disclosure refers to use of a molecule specifically recognizing an elastin receptor complex in the manufacture of a medicament for modulating an immune response comprising targeting cells having said complex associated with their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).

10 In one aspect, the present disclosure refers to a molecule specifically recognizing an elastin receptor complex for use in lowering autophagy, said molecule comprising a source of autophagy inhibiting 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.

15 In one aspect, the present disclosure refers to a molecule specifically recognizing an elastin receptor complex for use in the modulation of an immune response, said molecule comprising a source of autophagy inhibiting 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).

20 In one aspect, the present disclosure refers to a molecule specifically recognizing an elastin receptor complex for use in improving tissue repair, said molecule comprising a source of autophagy inhibiting 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).

25 In one aspect, the present disclosure refers to a molecule specifically recognizing an elastin receptor complex for use in modifying vascular permeability, said molecule comprising a source of autophagy inhibiting 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).

30 In one aspect, the present disclosure refers to a peptide comprising xGxxPG and a peptide selected from a dipeptide comprising dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQQ, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), for use in lowering autophagy, wherein x represents a naturally occurring amino acid.

35 In one aspect, the present disclosure refers to use of a peptide comprising xGxxPG and a peptide selected from a dipeptide comprising dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQQ, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), in the manufacture of a medicament for lowering autophagy, wherein x represents a naturally occurring amino acid.

40 In one aspect, the present disclosure refers to a peptide comprising at least 7 amino acids and at most 30 amino acids comprising a sequence of the formula ϕn xGxxPG, or xGxxPG ϕn , or ϕn xGxxPG ϕm wherein x is a naturally occurring amino acid, ϕ is an autophagy inhibiting amino acid and n = an integer from 1 to 24 and m is an integer from 1-23, whereby n+m is no greater than 24.

45 In one aspect, the present disclosure refers to a pharmaceutical formulation comprising a peptide comprising xGxxPG and a peptide selected from a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQQ, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), for use in lowering autophagy, wherein x represents a naturally occurring amino acid and at least one pharmaceutically acceptable excipient.

50 In one aspect, the present disclosure refers to use of a pharmaceutical formulation comprising a peptide comprising xGxxPG and a peptide selected from a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQQ, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), and at least one pharmaceutically acceptable excipient, in the manufacture of a medicament for lowering autophagy, wherein x represents a naturally occurring amino acid.

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

In one aspect, the present disclosure refers to a pharmaceutical formulation disclosed herein for use in the treatment of impairment of pancreatic beta-cell function.

In one aspect, the present disclosure refers to use of a pharmaceutical formulation disclosed herein in the manufacture of a medicament for treating impairment of pancreatic beta-cell function.

In one aspect, the present disclosure refers to a method for producing a peptide disclosed herein comprising synthesizing said peptide with an automated peptide synthesizer.

In one aspect, the present disclosure refers to a peptide disclosed herein obtainable with a method disclosed herein for any one of the uses disclosed herein.

In one aspect, the present disclosure refers to use of a peptide disclosed herein obtainable with a method disclosed herein in the manufacture of a medicament for any one of the uses disclosed herein.

Description

According to the present invention the amino acids that have the beneficial effects are targeted to the cells in which they can have their beneficial effects, in particular by targeting the elastin receptor complex through any specific means. Preferably the targeting means enables internalization of the amino acids and when the amino acids are provided in an oligopeptide format said internalization typically results in the oligopeptide being delivered to a lysosome (generally, and herein, also called autophagosome). Thus the invention provides a method for lowering autophagy, comprising targeting cells having an elastin receptor complex associated with their surface with a molecule specifically recognizing said complex, whereby said molecule is provided with a source of autophagy inhibiting 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), more preferably selected from the group leucine (L), alanine (A), glutamine (Q), glycine (G) and proline (P). Said targeting then results in delivering said source, as a package of autophagy inhibiting amino acids, to the cell, where the molecule provided with said source or package is for example

Claims

1. ~~A method for lowering autophagy, comprising targeting cells having an elastin receptor complex associated with their surface with~~Use of a molecule specifically
5 recognizing ~~an elastin receptor complex~~said complex, in the manufacture of a medicament for lowering autophagy comprising targeting cells having said complex associated with their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).
- 10
2. ~~A method for modifying vascular permeability, comprising targeting cells having an elastin receptor complex associated with their surface with~~Use of a molecule specifically
recognizing ~~an elastin receptor complex~~said complex, in the manufacture of a medicament for modifying vascular permeability comprising targeting cells having said complex
15 associated with their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).
- 20
3. ~~A method for improving tissue repair, comprising targeting cells having an elastin receptor complex associated with their surface with~~Use of a molecule specifically
recognizing ~~an elastin receptor complex~~said complex, in the manufacture of a medicament for improving tissue repair comprising targeting cells having said complex associated with
25 their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).
- 30
4. ~~A method for modulating an immune response, comprising targeting cells having an elastin receptor complex associated with their surface with~~Use of a molecule specifically
recognizing ~~an elastin receptor complex~~said complex, in the manufacture of a medicament for modulating an immune response comprising targeting cells having said complex
30 associated with their surface, whereby said molecule is provided with a source of autophagy inhibiting 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).

5. A usemethod according to any one of claims 1-4, wherein said molecule recognizing said complex has an elastin peptide motif represented by xGxxPG, wherein x represents a naturally occurring amino acid.
6. A usemethod according to any one of claims 1- 5, wherein said source of autophagy inhibiting amino acids is a peptide comprising said autophagy inhibiting amino acids.
7. A usemethod according to claim 6, wherein said peptide comprising said autophagy inhibiting amino acids comprises a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV).
8. A usemethod according to claim 6 or 7, wherein xGxxPG is connected to said peptide comprising said autophagy inhibiting amino acids by a peptide bond.
9. A usemethod according to any one of claims 1-4, wherein said molecule recognizing said complex is an antibody-like molecule, preferably selected from IgG, IgM, single chain antibodies, FAB- or FAB'2-fragments.
10. A usemethod according to claim 9 wherein said source of autophagy inhibiting amino acids is a peptide comprising a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), connected to said antibody-like molecule through a peptide bond.
11. A usemethod according to claim 9, wherein said antibody-like molecule is conjugated to said source of autophagy inhibiting amino acids.

12. A usemethod according to claim 9, wherein said source of autophagy inhibiting amino acids is a lipid vesicle such as a liposome.
13. A usemethod according to claim 12, wherein said liposome comprises a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV).
14. A molecule specifically recognizing an elastin receptor complex for use in lowering autophagy, said molecule comprising a source of autophagy inhibiting 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.
15. A molecule specifically recognizing an elastin receptor complex for use in the modulation of an immune response, said molecule comprising a source of autophagy inhibiting 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).
16. A molecule specifically recognizing an elastin receptor complex for use in improving tissue repair, said molecule comprising a source of autophagy inhibiting 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).
17. A molecule specifically recognizing an elastin receptor complex for use in modifying vascular permeability, said molecule comprising a source of autophagy inhibiting 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).
18. A molecule for a use according to any one of claims 14-17, wherein said molecule comprises an elastin peptide motif represented by xGxxPG, wherein x represents a naturally occurring amino acid.

19. A molecule for use according to any one of claims 14-17, wherein said molecule comprises an antibody-like molecule, selected from IgG, IgM, single chain antibodies, FAB- or FAB'2-fragments.
- 5 20. A molecule for use according to any one of claims 14-19, wherein said source of autophagy inhibiting amino acids is a peptide comprising a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV).
- 10 21. A molecule for use according to claim 20, wherein said molecule is connected to said peptide through a peptide bond.
22. A peptide comprising xGxxPG and a peptide selected from a dipeptide comprising
 15 dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), for use in lowering autophagy, wherein x represents a naturally occurring amino acid.
- 20 23. A peptide comprising at least 7 amino acids and at most 30 amino acids comprising a sequence of the formula ϕ^n xGxxPG, or xGxxPG ϕ^n , or ϕ^n xGxxPG ϕ^m wherein x is a naturally occurring amino acid, ϕ is an autophagy inhibiting amino acid and n = an integer from 1 to 24 and m is an integer from 1-23, whereby n+m is no greater than 24.
- 25 24. A peptide according to claim 23 wherein ϕ^n and/or ϕ^m comprise(s) a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV).
- 30 25. A pharmaceutical formulation comprising a peptide comprising xGxxPG and a peptide selected from a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG,

QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), for use in lowering autophagy, wherein x represents a naturally occurring amino acid and at least one pharmaceutically acceptable excipient.

- 5 26. A pharmaceutical formulation comprising a peptide according to claim 23 or 24 and at least one pharmaceutically acceptable excipient.
27. A pharmaceutical formulation according to claim 25 or 26 further comprising insulin.
- 10 28. A pharmaceutical formulation according to claim 27 for use in the treatment of impairment of pancreatic beta-cell function.
29. A method for producing a peptide according to claim 23 or 24 comprising synthesizing said peptide with an automated peptide synthesizer.
- 15 30. A peptide according to claim 23 or 24 obtainable with a method according to claim 29 for use according to any one of claims 14-17.
- 20 31. Use of a peptide comprising xGxxPG and a peptide selected from a dipeptide comprising dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and SEQ ID NO: 2 (AQGV), in the manufacture of a medicament for lowering autophagy, wherein x represents a naturally occurring amino acid.
- 25 32. Use of a pharmaceutical formulation comprising a peptide comprising xGxxPG and a peptide selected from a dipeptide selected from the group AQ, LQ, PQ, VQ, GQ, a tripeptide selected from the group AQL, LQL, PQL, VQL, GQL, PLQ, LQG, PQV, VGQ, LQP, LQV, AQG, QPL, PQV, VGQ, GQG or a tetrapeptide selected from the group SEQ ID NO: 1 (LQGV) and
- 30 SEQ ID NO: 2 (AQGV), and at least one pharmaceutically acceptable excipient, in the manufacture of a medicament for lowering autophagy, wherein x represents a naturally occurring amino acid.

33. Use of a pharmaceutical formulation according to claim 27 in the manufacture of a medicament for treating impairment of pancreatic beta-cell function.

34. Use of a peptide according to claim 23 or 24 obtainable with a method according to claim 29 in the manufacture of a medicament for use according to any one of claims 1-4.