

PEPTIDE COMPOUNDS AND METHODS OF TREATING DISEASES USING SAME

RELATED APPLICATION

5 This application claims the benefit of priority of Israeli Application No. 272074 filed on 15 January 2020, the contents of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING STATEMENT

10 The ASCII file, entitled 84727 SequenceListing.txt, created on 13 January 2021, comprising 12,288 bytes, submitted concurrently with the filing of this application is incorporated herein by reference.

FIELD AND BACKGROUND OF THE INVENTION

15 The present invention, in some embodiments thereof, relates to compositions and methods of using same for treating inflammatory and autoimmune diseases.

 There is an unmet need for novel compositions that may serve to attenuate cellular and immune stress-response in normal tissue, in a manner that is specific, safe and effective, thereby reducing the severity of stress associated degenerative diseases and stress-induced inflammation.

20 The peptide LPPLPYP (SEQ ID NO: 42, also known as Stressin-1 and IPL344) is a short 7 amino acids peptide that protects cells of various types from pro-apoptotic pressures and activates the Akt signaling system. The structure of IPL344 resembles the binding sites of adaptor proteins. It has been proposed to have a mechanism of action which comprises mimicking such proteins and activating cell protective processes via Akt and possibly other pathways.

25 International Patent Application Publication Nos: WO 2006/021954 and WO2012/160563 disclose the use of LPPLPYP (SEQ ID NO: 42) peptide for treating diseases such as ALS.

SUMMARY ~~OF THE INVENTION~~

 According to an aspect of the present ~~invention~~disclosure there is provided an isolated peptide being five or seven amino acids which consists of an amino acid sequence represented by the formula $X_1-X_2-X_3-X_4-X_5-X_6-X_7$ (SEQ ID NO: 45), wherein

30 (i) X_1 is selected from the group consisting of leucine, d-leucine, d-valine, d-arginine and absent;

 (ii) X_2 is selected from the group consisting of dimethylproline (dMP), proline, α -aminoisobutyric acid (Aib) and d-proline;

- (iii) X₃ is selected from the group consisting of dMP, proline Aib and d-proline;
- (iv) X₄ is selected from the group consisting of histidine, serine, valine, leucine, d-leucine and threonine;
- (v) X₅ is proline or alanine;
- 5 (vi) X₆ is selected from the group consisting of tyrosine, d-valine, d-aspartic acid, tryptophan and phenylalanine; and
- (vii) X₇ is selected from the group consisting of proline, dMP, d-proline and absent the peptide is capable of reducing the amount of dexamethasone-induced spleen and/or thymus weight loss in a mouse, with the proviso that the peptide does not consist of the sequence
- 10 as set forth in SEQ ID NOs 42, 43 or 44.

According to an aspect of the present ~~invention~~disclosure there is provided a pharmaceutical composition comprising the peptide disclosed herein as an active agent and a physiologically acceptable carrier.

According to an aspect of the present ~~invention~~disclosure there is provided an isolated peptide
15 being no longer than ten amino acids which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-33 and 34, wherein the peptide is capable of reducing the amount of dexamethasone-induced spleen and/or thymus weight loss in a mouse.

According to ~~embodiment~~examples of the present ~~invention~~disclosure, the peptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOs: 6-33 and 34.

20 According to ~~embodiment~~examples of the present ~~invention~~disclosure, the peptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOs: 6-12 and 13.

According to ~~embodiment~~examples of the present ~~invention~~disclosure, the peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-4 and 5.

25 According to ~~embodiment~~examples of the present ~~invention~~disclosure, the peptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-33 and 34.

According to ~~embodiment~~examples of the present ~~invention~~disclosure, the peptide is a stapled peptide.

According to ~~embodiment~~examples of the present ~~invention~~disclosure, the peptide is a cyclic peptide.

30 According to ~~embodiment~~examples of the present ~~invention~~disclosure, the order of the sequence is reversed and all of the amino acids are of the D-type.

According to ~~embodiment~~examples of the present ~~invention~~disclosure, the peptide is attached to a cell penetrating moiety.

35 According to ~~embodiment~~examples of the present ~~invention~~disclosure, the cell penetrating moiety is attached to an N-terminus of the peptide.

In another aspect, the present disclosure relates to a use of the isolated peptide as described herein in the manufacture of a pharmaceutical composition for treating disease associated with apoptosis. According to embodimentexamples of the present inventiondisclosure, the peptide is for use in treating a disease associated with apoptosis.

According to embodimentexamples of the present inventiondisclosure, the disease associated with apoptosis is an inflammatory or degenerative disease.

According to embodimentexamples of the present inventiondisclosure, the inflammatory disease is an autoimmune disease.

According to embodimentexamples of the present inventiondisclosure, the degenerative disease is a neurodegenerative disease.

According to embodimentexamples of the present inventiondisclosure, the disease associated with apoptosis is selected from the group consisting of age-related macular degeneration (AMD), retinitis pigmentosa, stroke and myocardial infarction.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the inventiondisclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodimentexamples of the inventiondisclosure, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to compositions and methods of using same for treating inflammatory and autoimmune diseases.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

The multi-proline peptide LPPLPYP (SEQ ID NO: 42), also known as IPL344 and Stressin-1) is a short 7 amino acids peptide that protects cells of various types from pro-apoptotic pressures and activates the Akt signaling system. It is a candidate for treating degenerative, inflammatory and autoimmune diseases.

Whilst researching the contribution of the individual amino acids of the peptide, the present inventors surprisingly found that particular amino acid replacements of the core sequence showed a significant improvement in reduction of the amount of dexamethasone-induced spleen and/or thymus weight loss in mice, whereas other replacements and/or deletions severely diminished the

WHAT IS CLAIMED IS:

1. An isolated peptide being five or seven amino acids which consists of an amino acid sequence represented by the formula $X_1-X_2-X_3-X_4-X_5-X_6-X_7$ (SEQ ID NO: 45), wherein

(i) X_1 , is selected from the group consisting of leucine, d-leucine, d-valine, d-arginine and absent;

(ii) X_2 is selected from the group consisting of dimethylproline (dMP), proline, α -aminoisobutyric acid (Aib) and d-proline;

(iii) X_3 is selected from the group consisting of dMP, proline Aib and d-proline;

(iv) X_4 is selected from the group consisting of histidine, serine, valine, leucine, d-leucine and threonine;

(v) X_5 is proline or alanine;

(vi) X_6 is selected from the group consisting of tyrosine, d-valine, d-aspartic acid, tryptophan and phenylalanine; and

(vii) X_7 is selected from the group consisting of proline, dMP, d-proline and absent
the peptide is capable of reducing the amount of dexamethasone-induced spleen and/or thymus weight loss in a mouse, with the proviso that the peptide does not consist of the sequence as set forth in SEQ ID NOs 42, 43 or 44.

2. The isolated peptide of claim 1, consisting of the amino acid sequence selected from the group consisting of SEQ ID NOs: 6-33 and 34.

3. The isolated peptide of claim 1, consisting of the amino acid sequence selected from the group consisting of SEQ ID NOs: 6-12 and 13.

4. An isolated peptide being no longer than ten amino acids which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-33 and 34, wherein the peptide is capable of reducing the amount of dexamethasone-induced spleen and/or thymus weight loss in a mouse.

5. The isolated peptide of claim 4, comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-4 and 5.

6. The isolated peptide of claim 4, consisting of the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-33 and 34.

7. The isolated peptide of any one of claims 1-6, wherein the peptide is a stapled peptide.

8. The isolated peptide of any one of claims 1-6, wherein the peptide is a cyclic peptide.

9. The isolated peptide of claim 4, wherein the order of the sequence is reversed and all of the amino acids are of the D-type.

10. The isolated peptide of any one of claims 1-~~9~~⁶, wherein the peptide is attached to a cell penetrating moiety.

11. The isolated peptide of claim 10, wherein said cell penetrating moiety is attached to an N-terminus of the peptide.

12. Use of tThe isolated peptide of any one of the claims 1-~~11~~⁶ ~~for use in the~~ manufacture of a pharmaceutical composition for treating disease associated with apoptosis.

13. The ~~isolated peptide~~use of claim 12, wherein said disease associated with apoptosis is an inflammatory or degenerative disease.

14. The ~~isolated peptide~~use of claim 13, wherein the inflammatory disease is an autoimmune disease.

15. The ~~isolated peptide~~use of claim 13, wherein said degenerative disease is a neurodegenerative disease.

16. The ~~isolated peptide~~use of claim 12, wherein said disease associated with apoptosis is selected from the group consisting of age-related macular degeneration (AMD), retinitis pigmentosa, stroke and myocardial infarction.

17. A pharmaceutical composition comprising the peptide of any one of claims 1-11 as an active agent and a physiologically acceptable carrier.