The present disclosure thus relates to a proteasome inhibitor for use for treating and/or preventing a disorder related to an accumulation of a non-degraded abnormal protein, such as a truncated and/or farnesylated prelamin A, particularly leading to a premature ageing disorder.

Preferably, the proteasome inhibitor is for use for treating and/or preventing a disorder related to an accumulation of a non-degraded abnormal protein, such as truncated and/or farnesylated prelamin A leading to a premature ageing disorder, by downregulating SRSF1.

The present disclosure also relates to a method for treating and/or preventing a disorder related to an accumulation of a non-degraded abnormal protein, such as truncated and/or farnesylated prelamin A leading to a premature ageing disorder, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a proteasome inhibitor.

The present invention also relates to the dermatologic, dermocosmetic or cosmetic use of a proteasome inhibitor for preventing and/or attenuating skin ageing, particularly human skin ageing. The invention also relates to the use of a proteasome inhibitor for attenuating physiological ageing, such as progerin- and/or farnesylated prelamin A-linked physiological ageing.

The disclosure also relates to the use of proteasome inhibitors in the treatment and/or prevention of age-related disorders and their metabolic consequences, in particular those including tissues expressing progerin and/or farnesylated prelamin A, such as skin, adipose tissue, bone, blood vessels and their endothelial and vascular smooth muscle cells and their consequences on skin, heart, brain or kidney.

In one aspect, there is provided the use of a proteasome inhibitor in the manufacture of a medicament for treating and/or preventing a disorder related to an accumulation of a non-degraded abnormal protein or a cancer.

In another aspect, there is provided the use of a proteasome inhibitor in the manufacture of a medicament for treating and/or preventing age-related disorders and their metabolic consequences, said age-related disorder being preferably chosen from osteoporosis, diabetes of type 2 and atherosclerosis.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the term "proteasome inhibitor" is a compound which blocks the enzymatic activity of proteasome. Mammalian 26S cytosolic and nuclear proteasome is made of one 20S proteolytic core and two 19S regulatory cap subunits (*36*). The 20S core provides a barrel-shaped cavity in which proteins are degraded.

The 20S core is made of four rings, two α and two β. Each α-ring comprises seven distinct α-subunit encoded by 7 genes, and each β-ring comprises seven distinct β- subunits encoded by 7 genes.

The 19S regulatory cap subunit is composed of a base comprising 6 ATPases and 2 non-

CLAIMS

1. Use of a proteasome inhibitor in the manufacture of a medicament for treating and/or preventing a disorder related to an accumulation of a non-degraded abnormal protein or a cancer.

2. The use according to claim 1, wherein said medicament downregulates SRSF1.

3. The use according to claim 1 or 2, wherein said non-degraded abnormal protein is chosen from truncated and/or farnesylated prelamin A, truncated and/or farnesylated B-type lamin, and proteins produced by a duplication of *LMNB1* and/or *LMNB2*.

4. The use according to any one of claims 1 to 3, wherein said disorder is chosen from premature ageing disorders, striated muscle disorders and neurodegenerative diseases.

5. The use according to any one of claims 1 to 4, wherein the proteasome inhibitor is chosen from peptides, optionally modified.

6. The use according to any one of claims 1 to 5, wherein the proteasome inhibitor is chosen from tripeptides, optionally modified.

7. The use according to any one of claims 1 to 6, wherein the proteasome inhibitor is chosen from tripeptides, optionally modified, comprising at least two leucine.

8. The use according to any one of claims 1 to 7, wherein the proteasome inhibitor is chosen from MG132, MG115, MG262 and MG110.

9. The use according to any one of claims 1 to 8, wherein the proteasome inhibitor is chosen from MG115, MG262 and MG110.

10. The use according to any one of claims 1 to 9, wherein said disorder is chosen from progeroid syndromes, striated muscle disorders and neurodegenerative diseases, or for treating and/or preventing a cancer.

11. The use according to any one of claims 1 to 10, wherein said disorder is chosen from progeroid syndromes and oculopharyngeal muscular dystrophy, or for treating and/or preventing a cancer.

12. The use according to any one of claims 1 to 11, wherein said disorder is chosen from Hutchinson-Gilford progeria syndrome, atypical progeria syndrome, restrictive dermopathy, Nestor-Guillermo progeria syndrome, Werner syndrome, Bloom syndrome, Rothmund-Thomson syndrome, Cockayne syndrome, *Xeroderma pigmentosum* and trichothiodystrophy.

13. Dermatological, dermocosmetic or cosmetic use of a proteasome inhibitor for preventing and/or attenuating skin ageing, particularly human skin ageing.

14. Use of a proteasome inhibitor for attenuating physiological ageing.

15. Use of a proteasome inhibitor in the manufacture of a medicament for treating and/or preventing age-related disorders and their metabolic consequences, said age-related disorder being preferably chosen from osteoporosis, diabetes of type 2 and atherosclerosis.