SUMMARY OF THE INVENTION

The present ~~invention~~ disclosure relates to the prophylactic or therapeutic use of the RNA sequences of interest for which the inventors have demonstrated particular involvement in the mechanisms of aging. They have especially shown the ability of these sequences to spectacularly increase the lifespan of a subject by stopping the mechanisms of aging and fighting the harmful effects associated therewith. The sequences ~~of the invention~~disclosed herein also fight diseases associated with aging such as degenerative diseases, laminopathies and cancers, as well as diabetes and obesity. They have proven especially effective in the treatment of infertility or sterility (i.e., difficulty conceiving or inability to conceive) as well as increasing the resistance of subjects, in particular subjects who have reached sexual maturity, preferably elderly subjects, to stress.

~~A first subject~~One aspect of the invention relates to an isolated or synthetic RNA sequence comprising sequence SEQ ID NO: 1, a homologous sequence, preferably an orthologous sequence, or a functionally analogous sequence, for use as a medicament.

The inventors have demonstrated that the RNA sequence SEQ ID NO: 1 discovered in Drosophila corresponds to orthologous sequences in mammals such as primates and human being, and in rodents such as mice and rats. The ~~invention~~ disclosure also covers the use, in one or the other of the applications described in this text, of an isolated or synthetic RNA sequence preferably chosen from among sequence SEQ ID NO: 2 of human origin and sequences SEQ ID NO: 3 and SEQ ID NO: 4 of mouse origin. Sequences SEQ ID NO: 2, 3, 4, 9, 11, 13, 15, 17, 19, 21, 22, 24, 26, and 28 identified in Table 1 of this text are examples of sequences orthologous to SEQ ID NO: 1.

Another ~~subject of the invention~~aspect is a DNA sequence coding for a RNA sequence of interest ~~according to the invention~~as disclosed herein.

The ~~invention~~ disclosure also concerns a vector permitting *in vitro*, *ex vivo* or *in vivo* expression of a RNA sequence ~~according to the invention~~disclosed herein. In one aspect, there is provided a vector allowing the expression of an RNA sequence as disclosed herein, chosen, for example, from among a plasmid, a cosmid, a viral vector and a phage, preferably comprising a promotor and/or regulator elements promoting the expression of the RNA sequence in intestinal or ovarian cells.

~~The invention also~~Another aspect concerns a cell comprising a RNA sequence ~~according to the invention~~as disclosed herein or transformed by a vector ~~according to the invention~~as disclosed herein, as well as a composition comprising a ~~product~~ RNA sequence, vector or cell as disclosed herein ~~according to the invention~~ and a dietarily- or pharmaceutically-acceptable support.

~~The invention also~~Another aspect concerns the use of a RNA sequence, vector, cell or a composition according to the invention, continuously or sequentially, to restore or modulate the expression of said RNA sequence *in vivo*, *in vitro* or *ex vivo*.

Another ~~object of the invention~~aspect relates to ~~is~~ a transgenic mouse whose genome has been genetically modified to prevent or modify, preferably alter, the expression of a RNA sequence of interest ~~according to the invention~~as disclosed herein, typically one and/or the other of sequences SEQ ID NO: 3 and SEQ ID NO: 4.

The ~~invention~~ disclosure also covers a method for evaluating the cosmetic or therapeutic efficacy of a test compound to fight the harmful effects of aging or stress, or to fight infertility, said method comprising i) exposure of a cell or population of cells not expressing the RNA sequence ~~of the invention~~disclosed herein or expressing an abnormal version of said RNA sequence; or a transgenic mouse ~~according to the invention~~as disclosed herein, ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell(s) or said transgenic mouse, and iii) determination of the cosmetic or therapeutic efficacy of said test compound, a restoration of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

The ~~invention~~ disclosure also covers a method for evaluating the cosmetic or therapeutic efficacy of a test compound to fight the harmful effects of aging or stress, or to fight infertility, said method comprising i) exposure of a cell ~~according to the invention~~ comprising an RNA sequence ~~according to the invention~~as disclosed herein or a population of cells comprising a cell ~~according to the invention~~as disclosed herein; ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell or population of cells, and iii) determination of the cosmetic or therapeutic efficacy of said test compound, an increase of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

Another aspect relates to a method for evaluating the cosmetic efficacy of a test compound, said method comprising i) exposure to a test compound of a cell, or a population of cells, not expressing the RNA sequence as disclosed herein or expressing an abnormal version of said RNA sequence; or a transgenic mouse as disclosed herein, ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell(s) or said transgenic mouse, and iii) determination of the cosmetic efficacy of said test compound, restoration of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

Another aspect relates to a method for evaluating the therapeutic efficacy of a test compound to fight the harmful effects of aging or a stress, a laminopathy, diabetes, obesity or to fight infertility, said method comprising i) exposure to a test compound of a cell or population of cells not expressing the RNA sequence as disclosed herein or expressing an abnormal version of said RNA sequence; ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell(s), and iii) determination of the therapeutic efficacy of said test compound, a restoration of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

Another aspect provides a method for evaluating the cosmetic efficacy of a test compound, said method comprising i) exposure to a test compound of a cell as disclosed herein comprising a RNA sequence as disclosed herein or of a population of cells comprising a cell as disclosed herein, ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell or said population of cells, and iii) determination of the cosmetic efficacy of said test compound, increase of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

Another aspect relates to a method for evaluating the cosmetic efficacy of a test compound to fight the harmful effects of aging or a stress, a laminopathy, diabetes, obesity or to fight infertility, said method comprising i) exposure to a test compound of a cell as disclosed herein comprising an RNA sequence as disclosed herein or of a population of cells comprising a cell as disclosed herein, ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell or said population of cells, and iii) determination of the therapeutic efficacy of said test compound, increase of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

Another aspect relates to the use of the RNA sequence as disclosed herein in the preparation of a medicament for extending the lifespan of a subject, increasing stress resistance, or fighting the harmful effects of aging in a subject.

Another aspect relates to the use of the RNA sequence as disclosed herein in the preparation of a medicament for the prevention or treatment of a degenerative disease in a subject, in particular a neurodegenerative disease, a laminopathy, diabetes, obesity or cancer.

Another aspect relates to the use of the RNA sequence as disclosed herein in the preparation of a medicament for the treatment of infertility or stimulation of fertility in a subject.

The invention also concerns kits comprising nucleic acids, vectors, cassettes and/or cells such as described previously.

DETAILED DESCRIPTION

The invention results from the demonstration by the inventors of the influence of a small sequence of nucleolar DNA (snoRNA:Ψ28S–1153 called *"youth"*, identified in this text as SEQ ID NO: 1) on the lifespan of Drosophila. This snoRNA has been identified as part of a systematic screening of snoRNAs associated with the Drosophila genome (Huang et al., 2005) without any function being ascribed to it to date.

The inventors have characterized this sequence and notably shown that a genomic deletion of 632 base pairs of the F4 region of the Drosophila genome containing the snoRNA:Ψ28S–1153, shortens the lifespan of Drosophila by around 30%. They then demonstrated that the over–expression of this RNA sequence, for example using a transgene containing genomic DNA coding for this snoRNA, spectacularly increases the lifespan of Drosophila by around 100%. Flies overexpressing the RNA sequence of the invention live up to twice as long. Furthermore, the inventors have identified and detected the expression of orthologous *"youth"* sequences in mice and humans.

efficacy of said test compound, restoration of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

18. Method for evaluating the therapeutic efficacy of a test compound to fight the harmful effects of aging or a stress, a laminopathy, diabetes, obesity or to fight infertility, said method comprising i) exposure to a test compound of a cell or population of cells not expressing the RNA sequence according to one of claims 1 to 3 or expressing an abnormal version of said RNA sequence; ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell(s), and iii) determination of the therapeutic efficacy of said test compound, a restoration of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

19. Method for evaluating the cosmetic efficacy of a test compound, said method comprising i) exposure to a test compound of a cell according to claim 13 comprising a RNA sequence according to one of claims 1 to 3 or of a population of cells comprising a cell according to claim 13, ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell or said population of cells, and iii) determination of the cosmetic efficacy of said test compound, increase of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

20. Method for evaluating the cosmetic efficacy of a test compound to fight the harmful effects of aging or a stress, a laminopathy, diabetes, obesity or to fight infertility, said method comprising i) exposure to a test compound of a cell according to claim 13 comprising an RNA sequence according to one of claims 1 to 3 or of a population of cells comprising a cell according to claim 13, ii) evaluation of the effects, if any, of the test compound on the phenotype of said cell or said population of cells, and iii) determination of the therapeutic efficacy of said test compound, increase of the activity and/or expression of said RNA sequence being correlated with efficacy of said test compound.

21. Method according to one of claims 17 to 20, wherein the cell or population of cells exposed is of intestinal or ovarian origin.

22. Use of the RNA sequence according to any one of claims 1 to 4 in the preparation of a medicament for extending the lifespan of a subject, increasing stress resistance, or fighting the harmful effects of aging in a subject.

23. Use of the RNA sequence according to one of claims 1 to 5 in the preparation of a medicament for the prevention or treatment of a degenerative disease in a subject, in particular a neurodegenerative disease, a laminopathy, diabetes, obesity or cancer.

24. The use according to claim 23 wherein the cancer is a cancer induced by free radicals.

25. Use of the RNA sequence according to one of claims 1 to 3 in the preparation of a medicament for the treatment of infertility or stimulation of fertility in a subject.

26. The use according to one of claims 22 to 25, characterized in that the subject is an animal or insect, typically a mammal, preferably a human, even more preferably a subject not expressing the RNA sequence according to one of claims 1 to 3 or expressing an abnormal version of said RNA sequence, a subject undergoing stress conditions such as fasting, heat shock or oxidative stress, and/or a subject suffering from a degenerative disease, a laminopathy, diabetes, obesity, a cancer or a fertility problem.

27. The use according to claim 26, characterized in that the genome of the subject, not expressing the RNA according to one of claims 1 to 3 or expressing an abnormal version of said RNA sequence, contains a DNA sequence comprising a mutation, said sequence being in the wild state chosen from among SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8; and said mutation being preferably chosen from among a deletion, substitution or addition of one or more base pairs.