SUMMARY OF THE INVENTION

The present 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 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.

One aspect of the invention relates to an isolated or synthetic RNA sequence comprising sequence SEQ ID NO: 1, a SEQ ID NO:1 orthologous sequence, or a SEQ ID NO:1 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 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 aspect is a DNA sequence coding for a RNA sequence of interest as disclosed herein.

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

Another aspect concerns a cell comprising a RNA sequence as disclosed herein or a cell transformed by a vector as disclosed herein, as well as a composition comprising a RNA sequence, vector or cell as disclosed herein and a dietarily- or pharmaceutically–acceptable support for use as a medicament.

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

The 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 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 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 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 comprising an RNA sequence as disclosed herein or 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 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.

Also disclosed is 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.

Also disclosed is 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.

Also disclosed is 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.

Also disclosed is 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 neurodegenerative disease induced by mutation of the fah2 gene, 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.

CLAIMS

1. Isolated or synthetic RNA sequence comprising sequence SEQ ID NO: 1, a SEQ ID NO:1 orthologous sequence or SEQ ID NO: 1 functionally–analogous sequence for use as a medicament.

2. RNA sequence for use according to claim 1, characterized in that said orthologous sequence is of human origin and consists in sequence SEQ ID NO: 2 or is of mouse origin and consists in a sequence chosen from among SEQ ID NO: 3 and SEQ ID NO: 4.

3. RNA sequence for use according to claim 1 or 2, characterized in that said sequence is a small nucleolar RNA (snoRNA).

4. RNA sequence for use according to claim 1, characterized in that said functionally–analogous sequence permits splicing a *Drosophila melanogaster* gene chosen from among Ir56d, buttonhead, klarsicht, CG3262, CG30502 (*fa2h*), CG11125, CG9339 and CG40006.

5. DNA sequence coding for an RNA sequence according to one of claims 1 to 4 for use as a medicament.

6. Vector allowing the expression of an RNA sequence according to one of claims 1 to 4 for use as a medicament, wherein the vector is chosen, for example, from among a plasmid, a cosmid, a viral vector and a phage, and wherein the vector preferably comprises a promotor and/or regulator elements promoting the expression of said RNA sequence in intestinal or ovarian cells.

7. Cell comprising a RNA sequence according to one of claims 1 to 4 for use as a medicament or cell transformed using a vector as described in claim 6 for use as a medicament.

8. Composition comprising a RNA sequence for use according to one of claims 1 to 4, a vector for use according to claim 6 or a cell according to claim 7 and a dietarily- or pharmaceutically–acceptable support.

9. Use of a RNA sequence according to one of claims 1 to 4, of a vector according to claim 6, of a cell according to claim 7 or of a composition according to claim 8, continuously or sequentially, to restore or modulate the expression of said RNA sequence *in vitro* or *ex vivo*.

10. Transgenic mouse in the genome of which one and/or the other of sequences SEQ ID NO: 3 and SEQ ID NO: 4 have been modified to prevent or modify the expression of one and/or the other of said sequences.

11. 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.

12. Use of the RNA sequence according to one of claims 1 to 4 in the preparation of a medicament for the prevention or treatment of a neurodegenerative disease induced by mutation of the fah2 gene in a subject, a laminopathy, diabetes, obesity or cancer.

13. The use according to claim 12 wherein the cancer is a cancer induced by free radicals.

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

15. The use according to one of claims 11 to 14, 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 neurodegenerative disease induced by mutation of the fah2 gene, a laminopathy, diabetes, obesity, a cancer or a fertility problem.

16. The use according to claim 15, 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.