

obesity, laminopathies such as Hutchinson Gilford's progeria, hernia, sarcopenia and cachexia, arthritis, scoliosis and cancer.

It was recently shown that clearance of senescent cells in a genetic fashion could markedly improve the fitness and decrease parameters of aging in a mouse model for accelerated aging. These mice showed reduced signs of aging measured by kyphosis (excessive bone curvature), muscle strength, fat deposition and cataracts. This provided further evidence that cellular senescence and the SASP is causally linked to age-associated phenotypes and cancer (Baker et al., 2011. Nature 479(7372):232-6). This proof-of-concept evidence was obtained in a genetic fashion that has poor therapeutic applicability.

It is clear in the context of the above that there is a need in the art for compounds that selectively induce apoptosis in senescent cells, as cellular senescence is linked to degenerative (loss-of-function) diseases and cancer (gain of function). There are currently no suitable therapeutically applicable compounds that can selectively induce apoptosis in senescent cells in vivo. It is a goal of the present invention to provide new and existing compounds that therapeutically target senescent cells and that can be used in the treatment of diseases associated with cellular senescence.

20

SUMMARY OF THE INVENTION

The inventors solved this problem by their unexpected finding that a peptide according to the disclosure, and the inhibitors NQDI and R406 for use according to the disclosure, selectively induce apoptosis in senescent cells and, as a consequence, are applicable in the treatment of diseases associated with the presence of senescent cells. The inventors showed *inter alia* that compounds according to the disclosure are effective in the (i) removal of senescent cells *in vitro*, *ex vivo* and *in vivo* (ii) countering symptoms of aging and age-related diseases in a fast aging mouse model, (iii) protection of organ function in an *in vivo* model for chemotherapy-

30

induced toxicity and (iv) sensitization of a resistant cancer to a chemotherapeutic agent it was previously resistant to or acquired resistance to.

Thus, in one aspect, the present invention provides a peptide
5 comprising the amino acid sequence
LTLRKEPASEIAQSILEAYSQNGWANRRSSGGKRP, wherein the amino acids in said amino acid sequence are D-amino acid residues.

In another aspect, the present invention provides a pharmaceutical composition comprising a peptide disclosed herein, optionally further
10 comprising a chemotherapeutic agent.

In yet another aspect, the present invention provides a retro-inverso peptide of the Forkhead box protein O4, preferably wherein the amino acid sequence of said Forkhead box protein O4 is indicated in Figs 14 or 15, or a homologue or a fragment thereof, wherein said homologue has an amino
15 acid sequence identity of at least 70% to the retro-inverso amino acid sequence of the Forkhead box protein O4, wherein said homologue exhibits apoptosis-inducing activity in senescent cells or cells having an increased FOXO4 expression as compared to a control cell and expressing pSer15-p53, and wherein said fragment has apoptosis-inducing activity in senescent cells
20 or cells having an increased FOXO4 expression as compared to a control cell and expressing pSer15-p53.

In yet another aspect, the present invention provides a nucleic acid encoding a peptide disclosed herein, optionally comprised in an expression vector.

25 In yet another aspect, the present invention provides a host cell comprising the nucleic acid disclosed herein.

In yet another aspect, the present invention provides the peptide disclosed herein, the pharmaceutical composition disclosed herein, or the nucleic acid disclosed herein, for use as a medicament, or for use in the
30 treatment of a disorder wherein it is beneficial to remove cells having an

increased FOXO4 expression as compared to a control cell and expressing pSer15-p53, preferably wherein said disorder is selected from the group of age-related disorders consisting of atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis;

5 glomerulosclerosis, diabetes including diabetes type I and II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia; (cardio)vascular diseases; myocardial infarction; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity;

10 boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or preventing graft failure after organ or tissue transplantation; ischemia reperfusion injury; hearing loss such as deafness;

15 vision loss such as blindness.

In yet another aspect, the present invention provides the peptide disclosed herein, the pharmaceutical composition disclosed herein, or the nucleic acid disclosed herein, for use as a medicament, or for use in the treatment of a disorder wherein the removal of senescent cells is beneficial,

20 preferably wherein said disorder is selected from the group of age-related disorders consisting of atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type I and II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS);

25 laminopathies; osteoporosis; dementia; (cardio)vascular diseases; myocardial infarction; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related

30 macular degeneration; COPD; asthma; renal insufficiency; reducing or

preventing graft failure after organ or tissue transplantation; ischemia reperfusion injury; hearing loss such as deafness; vision loss such as blindness.

In yet another aspect, the present invention provides the peptide disclosed herein, the pharmaceutical composition disclosed herein, or the nucleic acid disclosed herein for use in countering p21cip1 expression in a human subject, for use in removing cells that express p16INK4a in a subject, and/or for use in countering or in reducing the number of nuclear serine-15-phosphorylated p53 foci in a subject, whereby said subject is suffering from, or expected to suffer from atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type I and II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia; (cardio)vascular diseases; myocardial infarction; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or preventing graft failure after organ or tissue transplantation; ischemia reperfusion injury; hearing loss such as deafness; vision loss such as blindness.

More specifically, the inventors solved this problem by providing a peptide comprising the amino acid sequence LTLRKEPASEIAQSILEAYSQNGWANRRSGGKRP, wherein the amino acids in said amino acid sequence are D-amino acid residues.

Alternatively, provided is a peptide having at least 70%, preferably at least 90%, amino acid sequence identity to the peptide of claim 1, or a fragment of the peptide of claim 1, wherein said peptide or fragment exhibits apoptosis-inducing activity in senescent cells, preferably wherein

said fragment has the amino acid sequence SEIAQSILEAYSQNGW, and wherein at least 90% of the amino acids in said amino acid sequence or in said fragment are D-amino acid residues.

In a preferred example of a peptide of the disclosure, the peptide
5 further comprises a cell-penetrating peptide sequence, preferably said cell-penetrating peptide sequence has the amino acid sequence PPRRRQRRKKRG, preferably wherein the amino acids in said cell-penetrating peptide sequence are D-amino acid residues.

In yet another preferred example of a peptide of the disclosure,
10 further comprising a cell-penetrating peptide sequence, said cell-penetrating peptide is fused to the C-terminal part of said peptide.

Disclosed is a pharmaceutical composition comprising a peptide according to the disclosure.

In a preferred example of a pharmaceutical composition of the
15 disclosure, the pharmaceutical composition further comprises a chemotherapeutic agent.

Also disclosed is a retro-inverso peptide of the Forkhead box protein O4, preferably wherein the amino acid sequence of said Forkhead box protein O4 is indicated in Figs 14 or 15, or a homologue

or a fragment thereof, wherein said homologue has an amino acid sequence identity of at least 70% to the retro-inverso amino acid sequence of the Forkhead box protein O4, wherein said homologue exhibits apoptosis-inducing activity in senescent cells, and wherein said fragment has
5 apoptosis-inducing activity in senescent cells.

Also disclosed is a nucleic acid encoding a peptide according to the disclosure, optionally comprised in a vector.

Also disclosed is a host cell comprising a nucleic acid or vector according to the disclosure.

10 Also disclosed is a peptide, pharmaceutical composition, or nucleic acid according to the disclosure for use as a medicament, or for use in the treatment of a disorder wherein it is beneficial to remove cells having an increased FOXO4 expression as compared to a control, and expression of pSer15-p53 (active p53 signaling), preferably wherein said disorder is
15 selected from the group of age-related disorders consisting of atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type I and II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis;
20 dementia; (cardio)vascular diseases; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or
25 preventing graft failure after organ or tissue transplantation; incontinence; hearing loss such as deafness; vision loss such as blindness; sleeping disturbances; pain such as joint pain or leg pain; imbalance; fear; depression; breathlessness; weight loss; hair loss; muscle loss; loss of bone density; frailty and/or reduced fitness.

Also disclosed is a peptide, pharmaceutical composition, or nucleic acid according to the disclosure for use as a medicament, or for use in the treatment of a disorder wherein the removal of senescent cells is beneficial, preferably wherein said disorder is selected from the group of age-related disorders consisting of atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia; (cardio)vascular diseases; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or preventing graft failure after organ or tissue transplantation; incontinence; hearing loss such as deafness; vision loss such as blindness; sleeping disturbances; pain such as joint pain or leg pain; imbalance; fear; depression; breathlessness; weight loss; hair loss; muscle loss; loss of bone density; frailty and/or reduced fitness.

In another preferred example of a peptide, pharmaceutical composition, or nucleic acid for use according to the disclosure, the disorder is cancer, and wherein the use is for administration to a mammalian subject, preferably a human, before, during and/or after subjecting said subject to radiation therapy, and/or before, during or after administering to said subject at least one chemotherapeutic agent.

In still another preferred example of a peptide, pharmaceutical composition, or nucleic acid for use according to the disclosure, wherein said disorder is cancer, the cancer is a cancer resistant to therapy.

In yet another preferred example of a peptide, pharmaceutical composition, or nucleic acid for use according to the disclosure, wherein the

disorder is cancer and wherein the cancer is a cancer resistant to therapy, said therapy-resistant cancer is metastatic melanoma, breast cancer or glioblastoma, preferably metastatic melanoma, and wherein said therapy to which said cancer is resistant is radiation therapy and/or chemotherapy involving a RAF, MEK or ERK inhibitor or a composition comprising 5' FluoroUracil, Doxorubicin and Cyclofosfamide (FAC) as chemotherapeutic agent, preferably wherein said RAF, MEK or ERK inhibitor is RAF265, trametinib, dabrafenib, selumetinib, vemurafenib, cobemitinib and/or trametinib, more preferably vemurafenib and/or trametinib, and combinations thereof.

Also disclosed is a peptide, pharmaceutical composition, or nucleic acid according to the disclosure for use in removing senescent cells in a human subject suffering from, or expected to suffer from, atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including type II diabetes; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia; (cardio)vascular diseases; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or preventing graft failure after organ or tissue transplantation, ischemia-reperfusion injury, incontinence; hearing loss such as deafness; vision loss such as blindness; sleeping disturbances; pain such as joint pain or leg pain; imbalance; fear; depression; breathlessness; weight loss; hair loss; muscle loss; loss of bone density; frailty and/or reduced fitness.

Also disclosed is a peptide, pharmaceutical composition or nucleic acid according to the disclosure for

use in countering p21^{cip1} expression and/or removing cells that express p21^{cip1}, in a human subject suffering from, or expected to suffer from, atherosclerosis, chronic inflammatory diseases such as arthritis or athrosis, cancer, osteoarthritis, glomerulosclerosis, diabetes including type II

5 diabetes, diabetic ulcers, kyphosis, scoliosis, hepatic insufficiency, cirrhosis, Hutchinson-Gilford progeria syndrome (HGPS), laminopathies, osteoporosis, dementia, (cardio)vascular diseases, obesity, metabolic syndrome, acute myocardial infarction, emphysema, insulin sensitivity, boutonneuse fever, sarcopenia, neurodegenerative diseases such as Alzheimer's , Huntington's

10 or Parkinson's disease cataracts, anemia, hypertension, fibrosis, age-related macular degeneration, COPD, asthma, renal insufficiency, reducing or preventing graft failure after organ or tissue transplantation, incontinence, hearing loss such as deafness, vision loss such as blindness, sleeping disturbances, pain such as joint pain or leg pain, imbalance, fear,

15 depression, breathlessness, weight loss, hair loss, muscle loss, loss of bone density, frailty and/or reduced fitness.

Also disclosed is a peptide, pharmaceutical composition or nucleic acid according to the disclosure for use in countering p16INK4a expression and/or removing cells that express p16INK4a in a subject suffering from, or

20 expected to suffer from, atherosclerosis, chronic inflammatory diseases such as arthritis or athrosis, cancer, osteoarthritis, glomerulosclerosis, diabetes including type II diabetes, diabetic ulcers, kyphosis, scoliosis, hepatic insufficiency, cirrhosis, Hutchinson-Gilford progeria syndrome (HGPS), laminopathies, osteoporosis, dementia, (cardio)vascular diseases, obesity,

25 metabolic syndrome, acute myocardial infarction, emphysema, insulin sensitivity, boutonneuse fever, sarcopenia, neurodegenerative diseases such as Alzheimer's , Huntington's or Parkinson's disease cataracts, anemia, hypertension, fibrosis, age-related macular degeneration, COPD, asthma, renal insufficiency, reducing or preventing graft failure after organ or tissue

30 transplantation, incontinence,

hearing loss such as deafness, vision loss such as blindness, sleeping disturbances, pain such as joint pain or leg pain, imbalance, fear, depression, breathlessness, weight loss, hair loss, muscle loss, loss of bone density, frailty and/or reduced fitness.

5 Also disclosed is a peptide, pharmaceutical composition or nucleic acid according to the disclosure for use in countering, or reducing the number of, nuclear serine-15-phosphorylated p53 foci in a subject suffering, or expected to suffer, from atherosclerosis, chronic inflammatory diseases such as arthritis or athrosis, cancer, osteoarthritis, glomerulosclerosis, diabetes
10 including type II diabetes, diabetic ulcers, kyphosis, scoliosis, hepatic insufficiency, cirrhosis, Hutchinson-Gilford progeria syndrome (HGPS), laminopathies, osteoporosis, dementia, (cardio)vascular diseases, obesity, metabolic syndrome, acute myocardial infarction, emphysema, insulin sensitivity, boutonneuse fever, sarcopenia, neurodegenerative diseases such
15 as Alzheimer's, Huntington's or Parkinson's disease cataracts, anemia, hypertension, fibrosis, age-related macular degeneration, COPD, asthma, renal insufficiency, reducing or preventing graft failure after organ or tissue transplantation, incontinence, hearing loss such as deafness, vision loss such as blindness, sleeping disturbances, pain such as joint pain or leg pain,
20 imbalance, fear, depression, breathlessness, weight loss, hair loss, muscle loss, loss of bone density, frailty and/or reduced fitness.

 Also disclosed is a kit comprising a first container containing a peptide or nucleic acid according to the disclosure and a second container containing a chemotherapeutic agent.

25 Also disclosed is an inhibitor of ASK1 for use in the treatment of a disorder wherein the removal of senescent cells is beneficial.

 In a preferred example of an inhibitor of ASK1 for use according to the disclosure, the inhibitor of ASK1 is NQDI.

In another preferred example of an inhibitor of ASK1 for use according to the disclosure, the disorder is selected from the group of age-related disorders consisting of atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia; (cardio)vascular diseases; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or preventing graft failure after organ or tissue transplantation; incontinence; hearing loss such as deafness; vision loss such as blindness; sleeping disturbances; pain such as joint pain or leg pain; imbalance; fear; depression; breathlessness; weight loss; hair loss; muscle loss; loss of bone density; frailty and/or reduced fitness.

In yet another preferred example of an inhibitor of ASK1 for use according to the disclosure, the disorder is cancer; and wherein the use is for administration to a mammalian subject, preferably a human, before, during and/or after subjecting said subject to radiation therapy, and/or before, during or after administering to said subject at least one chemotherapeutic agent.

In still another preferred example of an inhibitor of ASK1 for use according to the disclosure, wherein the disorder is cancer, said cancer is a cancer resistant to therapy.

In still another preferred example of an inhibitor of ASK1 for use according to the disclosure, wherein the disorder is cancer and wherein the cancer is a cancer resistant to therapy, said cancer resistant to therapy is metastatic melanoma, breast cancer or glioblastoma, preferably metastatic melanoma, and wherein said therapy to which said cancer is resistant is

chemotherapy involving a RAF, MEK or ERK inhibitor as chemotherapeutic agent, preferably wherein said RAF, MEK or ERK inhibitor is RAF265, trametinib, dabrafenib, selumetinib, vemurafenib and/or trametinib, more preferably vemurafenib and/or trametinib.

5 Also disclosed is a pharmaceutical combination comprising an inhibitor of ASK1, preferably NQDI, and a chemotherapeutic agent.

 Also disclosed is a kit for use in medicine, preferably for use in the treatment of cancer, the kit comprising a first container containing an inhibitor of ASK1, preferably NQDI, and a second container containing a
10 chemotherapeutic agent.

 Also disclosed is an inhibitor of SYK for use in the treatment of a disorder wherein the removal of senescent cells is beneficial, wherein said disorder is not asthma, immune thrombocytopenia, hemolytic anemia, myeloid leukemia and/or lymphoma, preferably wherein said disorders are
15 those listed in claim 15.

 In a preferred example of an inhibitor of SYK for use according to the disclosure, the inhibitor of SYK is R406.

 In another preferred example of an inhibitor of SYK for use according to the disclosure, said disorder is cancer, and wherein the use is for
20 administration to a mammalian subject, preferably a human, before, during and/or after subjecting said subject to radiation therapy and/or before, during or after administering at least one chemotherapeutic agent to said subject, with the proviso that said cancer is not a lymphoma or leukemia, preferably not lymphoma or myeloid leukemia.

25 In yet another preferred example of an inhibitor of SYK for use according to the disclosure, wherein the disorder is cancer, the cancer is a cancer that is resistant to therapy.

 In yet another preferred example of an inhibitor of SYK for use according to the previous example, said cancer resistant to therapy is

metastatic melanoma, breast cancer or glioblastoma, preferably metastatic melanoma, and wherein said therapy to which said cancer is resistant is chemotherapy involving a RAF, MEK or ERK inhibitor as chemotherapeutic agent, preferably wherein said RAF, MEK or ERK inhibitor is RAF265, trametinib, dabrafenib, selumetinib, vemurafenib and/or trametinib, more preferably vemurafenib and/or trametinib.

Also disclosed is a pharmaceutical combination comprising an inhibitor of SYK, preferably R406, and a chemotherapeutic agent.

Also disclosed is a kit for use in medicine, the kit comprising a first container containing an inhibitor of SYK, preferably R406, and a second container containing a chemotherapeutic agent.

Also disclosed is a kit for use in the treatment of cancer, wherein the cancer is not a lymphoma or leukemia, preferably not lymphoma or myeloid leukemia, and wherein the kit comprises a first container containing an inhibitor of SYK, preferably R406, and a second container containing a chemotherapeutic agent.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows that the overall fitness of the *bubr1^{H/H} ink^{attac-3}* fast aging mouse model is significantly improved when senescent cells were genetically removed (mice above: senescent cells removed, mice below: senescent cells present). In parallel, these mice showed reduced signs of aging measured by kyphosis (excessive bone curvature), muscle strength, fat deposition and cataracts (Baker et al., 2011. Nature 479(7372):232-6). Senescence is thus causally linked to aging.

Figure 2 shows in panels A and B the sequence and 3D structure of FOXO4 used for the design of FOXO4 DRI which has the sequence: H-ltlrkepaseiaqsileaysqngwanrrsggkrpppprrrrqrrkkrgh-OH (MW: 5358.2), in

Claims

1. A peptide comprising the amino acid sequence
LTLRKEPASEIAQSILEAYSQNGWANRRRSGGKRP, wherein the amino acids
in said amino acid sequence are D-amino acid residues.
- 5 2. A peptide having at least 70%, preferably at least 90%, amino acid
sequence identity to the peptide of claim 1, or a fragment of the peptide of
claim 1, wherein said peptide or fragment exhibits apoptosis-inducing activity
in senescent cells or cells having an increased FOXO4 expression as compared
to a control cell and expressing Ser15 phosphorylated p53 (pSer15-p53),
10 preferably wherein said fragment has the amino acid sequence
SEIAQSILEAYSQNGW, and wherein at least 90% of the amino acids in said
amino acid sequence or in said fragment are D-amino acid residues.
3. A peptide according to claim 1 or 2, further comprising a cell-penetrating
15 peptide sequence, preferably said cell-penetrating peptide sequence has the
amino acid sequence PPRRRQRRKKRG, preferably wherein the amino acids in
said cell-penetrating peptide sequence are D-amino acid residues.
4. Peptide according to claim 3, wherein said cell-penetrating peptide is
20 fused to the C-terminal part of said peptide.
5. A pharmaceutical composition comprising a peptide according to any one
of claims 1-4, optionally further comprising a chemotherapeutic agent.
- 25 6. A retro-inverso peptide of the Forkhead box protein O4, preferably
wherein the amino acid sequence of said Forkhead box protein O4 is indicated
in Figs 14 or 15, or a homologue or a fragment thereof, wherein said homologue
has an amino acid sequence identity of at least 70% to the retro-inverso amino
acid sequence of the Forkhead box protein O4, wherein said homologue exhibits

apoptosis-inducing activity in senescent cells or cells having an increased FOXO4 expression as compared to a control cell and expressing pSer15-p53, and wherein said fragment has apoptosis-inducing activity in senescent cells or cells having an increased FOXO4 expression as compared to a control cell and
 5 expressing pSer15-p53.

7. A nucleic acid encoding a peptide according to any one of claims 1-4 or 6, optionally comprised in an expression vector.

10 8. A host cell comprising the nucleic acid according to claim 7.

9. The peptide of any one of claims 1-4 or 6, the pharmaceutical composition according to claim 5, or the nucleic acid according to claim 7, for use as a medicament, or for use in the treatment of a disorder wherein it is
 15 beneficial to remove cells having an increased FOXO4 expression as compared to a control cell and expressing pSer15-p53, preferably wherein said disorder is selected from the group of age-related disorders consisting of atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type I and II;
 20 diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia; (cardio)vascular diseases; myocardial infarction; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's,
 25 Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or preventing graft failure after organ or tissue transplantation; ischemia reperfusion injury; hearing loss such as deafness; vision loss such as blindness.

10. The peptide of any one of claims 1-4 or 6, the pharmaceutical composition according to claim 5, or the nucleic acid according to claim 7, for use as a medicament, or for use in the treatment of a disorder wherein the removal of senescent cells is beneficial, preferably wherein said disorder is
5 selected from the group of age-related disorders consisting of atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis; cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type I and II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia;
10 (cardio)vascular diseases; myocardial infarction; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity; boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing
15 or preventing graft failure after organ or tissue transplantation; ischemia reperfusion injury; hearing loss such as deafness; vision loss such as blindness.

11. The peptide of any one of claims 1-4 or 6, the pharmaceutical composition according to claim 5, or the nucleic acid according to claim 7 for
20 use in countering p21cip1 expression in a human subject, for use in removing cells that express p16INK4a in a subject, and/or for use in countering or in reducing the number of nuclear serine-15-phosphorylated p53 foci in a subject, whereby said subject is suffering from, or expected to suffer from
atherosclerosis; chronic inflammatory diseases such as arthritis or arthrosis;
25 cancer; osteoarthritis; glomerulosclerosis, diabetes including diabetes type I and II; diabetic ulcers; kyphosis; scoliosis; hepatic insufficiency; cirrhosis; Hutchinson-Gilford progeria syndrome (HGPS); laminopathies; osteoporosis; dementia; (cardio)vascular diseases; myocardial infarction; obesity; metabolic syndrome; acute myocardial infarction; emphysema; insulin sensitivity;

boutonneuse fever; sarcopenia; neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's disease; cataracts; anemia; hypertension; fibrosis; age-related macular degeneration; COPD; asthma; renal insufficiency; reducing or preventing graft failure after organ or tissue
5 transplantation; ischemia reperfusion injury; hearing loss such as deafness; vision loss such as blindness.