

Claims

1. A peptide comprising the amino acid sequence
LTLRKEPASEIAQSILEAYSQNGWANRRSGGKRP, 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
 5 cells having an increased FOXO4 expression as compared to a control cell and 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
 15 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 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;
 20 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
 25 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.

- 5 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 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; (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; 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.

- 25 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 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;

5 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;

10 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;

15 hair loss; muscle loss; loss of bone density; frailty and/or reduced fitness.

12. An inhibitor of ASK1 for use in the treatment of a disorder wherein the removal of senescent cells is beneficial, preferably wherein said inhibitor of ASK1 is NQDI, preferably wherein said disorder is selected from the group of

20 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; (cardio)vascular

25 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; 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
5 density; frailty and/or reduced fitness.

13. A pharmaceutical combination comprising an inhibitor of ASK1, preferably NQDI, and a chemotherapeutic agent.

10 14. 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 those listed in claim 11, preferably wherein said inhibitor of SYK is R406, and preferably wherein said
15 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 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.

20

15. A pharmaceutical combination comprising an inhibitor of SYK, preferably R406, and a chemotherapeutic agent.