

**CLAIMS**

1. A non-naturally occurring molecule configured to form an intermolecular beta-sheet with a human RAS protein mutated at position 12 or 13 and substantially not with wild-type human RAS protein.
- 5 2. The molecule according to claim 1, wherein the mutant human RAS protein is a G12V, G12C, G12A, or G12S mutant human RAS protein, preferably a G12V mutant human RAS protein, or is a G13V, G13C, or G13S mutant human RAS protein, preferably a G13V mutant human RAS protein.
3. The molecule according to claim 1 or 2, wherein the RAS protein is KRAS, NRAS or HRAS  
10 protein, preferably KRAS protein.
4. The molecule according to any one of claims 1 to 3, wherein the intermolecular beta-sheet involves the amino acid at position 12 or 13 of the mutant human RAS protein.
5. The molecule according to claim 4, wherein the intermolecular beta-sheet involves:
  - a) a portion of or the whole of the amino acid sequence TEYKLVVVGAVGVG (SEQ ID  
15 NO: 2) in the G12V mutant human RAS protein; or
  - b) a portion of or the whole of the amino acid sequence TEYKLVVVGACGVG (SEQ ID NO: 6) or preferably TEYKLVVVGACGV (SEQ ID NO: 3) in the G12C mutant human RAS protein; or
  - c) a portion of or the whole of the amino acid sequence TEYKLVVVGAAGVG (SEQ ID  
20 NO: 7) or preferably TEYKLVVVGAAGV (SEQ ID NO: 4) in the G12A mutant human RAS protein; or
  - d) a portion of or the whole of the amino acid sequence TEYKLVVVGASGVG (SEQ ID NO: 8) or preferably TEYKLVVVGASGV (SEQ ID NO: 9) or more preferably TEYKLVVVGASG (SEQ ID NO: 5) in the G12S mutant human RAS protein; or
  - 25 e) a portion of or the whole of the amino acid sequence TEYKLVVVGAGVVG (SEQ ID NO: 82) in the G13V mutant human RAS protein; or
  - f) a portion of or the whole of the amino acid sequence TEYKLVVVGAGCVG (SEQ ID NO: 84) or preferably TEYKLVVVGAGCV (SEQ ID NO: 81) in the G13C mutant human RAS protein; or

g) a portion of or the whole of the amino acid sequence TEYKLVVVGAGSVG (SEQ ID NO: 85) or preferably TEYKLVVVGAGSV (SEQ ID NO: 86) or more preferably TEYKLVVVGAGS (SEQ ID NO: 83) in the G13S mutant human RAS protein.

6. The molecule according to any one of claims 1 to 5, wherein the molecule is able to decrease the solubility or to induce the aggregation or inclusion body formation of the human RAS protein mutated at position 12 or 13.

7. The molecule according to any one of claims 1 to 6, wherein the molecule comprises an amino acid stretch which participates in the intermolecular beta-sheet.

8. The molecule according to claim 7, wherein the amino acid stretch comprises at least 6 contiguous amino acids of the amino acid sequence:

a) TEYKLVVVGAVGVG (SEQ ID NO: 2); or

b) TEYKLVVVGACGVG (SEQ ID NO: 6) or preferably TEYKLVVVGACGV (SEQ ID NO: 3); or

c) TEYKLVVVGAAGVG (SEQ ID NO: 7) or preferably TEYKLVVVGAAGV (SEQ ID NO: 4); or

d) TEYKLVVVGASGVG (SEQ ID NO: 8) or preferably TEYKLVVVGASGV (SEQ ID NO: 9) or more preferably TEYKLVVVGASG (SEQ ID NO: 5); or

e) TEYKLVVVGAGVVG (SEQ ID NO: 82); or

f) TEYKLVVVGAGCVG (SEQ ID NO: 84) or preferably TEYKLVVVGAGCV (SEQ ID NO: 81); or

g) TEYKLVVVGAGSVG (SEQ ID NO: 85) or preferably TEYKLVVVGAGSV (SEQ ID NO: 86) or more preferably TEYKLVVVGAGS (SEQ ID NO: 83);

including the amino acid at position 11 of the respective sequences a) to d), or the amino acid at position 12 of the respective sequences e) to g).

9. The molecule according to claim 7 or 8, wherein the molecule comprises the amino acid stretch VVVGAV (SEQ ID NO: 10), LVVVGAV (SEQ ID NO: 11), VVVGAVG (SEQ ID NO: 12), VVVGAVGVG (SEQ ID NO: 13), VVVGAGV (SEQ ID NO: 99), LVVVGAGV (SEQ ID NO: 100), VVVGAGVV (SEQ ID NO: 101) or VVVGAGVVG (SEQ ID NO: 102).

10. The molecule according to any one of claims 7 to 9, wherein the amino acid stretch comprises one or more D-amino acids and/or analogues of one or more of its amino acids.

11. The molecule according to any one of claims 7 to 10, wherein the molecule comprises two or more, preferably two, said amino acid stretches, which are identical or different.

12. The molecule according to any one of claims 7 to 11, wherein the amino acid stretch or stretches are each independently flanked, on each end independently, by one or more amino acids that display low beta-sheet forming potential or a propensity to disrupt beta-sheets.

13. The molecule according to any one of claims 7 to 12, wherein the molecule comprises, consists essentially of or consists of the structure:

a) NGK1-P1-CGK1,

b) NGK1-P1-CGK1-Z1-NGK2-P2-CGK2,

c) NGK1-P1-CGK1-Z1-NGK2-P2-CGK2-Z2-NGK3-P3-CGK3, or

d) NGK1-P1-CGK1-Z1-NGK2-P2-CGK2-Z2-NGK3-P3-CGK3-Z3-NGK4-P4-CGK4,

wherein:

P1 to P4 each independently denote an amino acid stretch as defined in any one of claims 7 to 10,

NGK1 to NGK4 and CGK1 to CGK4 each independently denote 1 to 4 contiguous amino acids that display low beta-sheet forming potential or a propensity to disrupt beta-sheets, such as 1 to 4 contiguous amino acids selected from the group consisting of R, K, D, E, P, N, S, H, G, Q, and A, D-isomers and/or analogues thereof, and combinations thereof, preferably 1 to 4 contiguous amino acids selected from the group consisting of R, K, D, E, P, N, S, H, G, and Q, D-isomers and/or analogues thereof, and combinations thereof, more preferably 1 to 4 contiguous amino acids selected from the group consisting of R, K, D, E, and P, D-isomers and/or analogues thereof, and combinations thereof, and

Z1 to Z3 each independently denote a direct bond or preferably a linker.

14. The molecule according to claim 13, wherein:

NGK1 to NGK4 and CGK1 to CGK4 is each independently 1 to 2 contiguous amino acids selected from the group consisting of R, K, A, and D, D-isomers and/or analogues thereof, and combinations thereof, preferably NGK1 to NGK4 and CGK1 to CGK4 is each independently 1 to 2 contiguous amino acids selected from the group consisting of R, K, and D, D-isomers and/or analogues thereof, and combinations thereof, such as wherein NGK1 to NGK4 and CGK1 to CGK4 is each independently K, R, D, A or KK, preferably each independently K, R, D or KK; and/or

each linker is independently selected from a stretch of between 1 and 10 units, preferably between 1 and 5 units, wherein a unit is each independently an amino acid or poly(ethylene glycol) (PEG), such as wherein each linker is independently GS, PP or GSGS (SEQ ID NO: 14), preferably GS, or D-isomers and/or analogues thereof.

- 5 15. The molecule according to claim 13 or 14, wherein the molecules comprises, consists essentially of or consists of a peptide of the amino acid sequence:

a) KVVVGAVKGSKVVVGAVK (SEQ ID NO: 15); or

b) KLVVVGAVKGSKLVVVGAVK (SEQ ID NO: 16); or

c) KVVVGAVGKGSKVVVGAVGK (SEQ ID NO: 17); or

10 d) KVVVGAVGVGKGSKVVVGAVGVGK (SEQ ID NO: 18); or

e) KVVVGAGVKGSKVVVGAGVK (SEQ ID NO: 128); or

f) KLVVVGAGVKGSKLVVVGAGVK (SEQ ID NO: 129); or

g) KVVVGAGVVKGSKVVVGAGVVK (SEQ ID NO: 130); or

h) KVVVGAGVVKGSKVVVGAGVVGK (SEQ ID NO: 131);

- 15 optionally wherein the amino acid sequence comprises one or more D-amino acids and/or analogues of one or more of its amino acids, optionally wherein the N-terminal amino acid is acetylated and/or the C-terminal amino acid is amidated.

16. The molecule according to any one of claims 1 to 15, which comprises a detectable label, a moiety that allows for isolation of the molecule, a moiety increasing the stability or half-life of the molecule, a moiety increasing the solubility of the molecule, a moiety increasing the cellular uptake of the molecule, and/or a moiety effecting targeting of the molecule to cells.

17. The molecule according to any one of claims 1 to 16 for use in medicine; or

a nucleic acid encoding the molecule according to any one of claims 1 to 16, wherein the molecule is a polypeptide, for use in medicine.

- 25 18. The molecule according to any one of claims 1 to 16 for use in a method of treating a disease caused by or associated with a mutation at position 12 or 13 in human RAS protein; or

a nucleic acid encoding the molecule according to any one of claims 1 to 16, wherein the molecule is a polypeptide, for use in a method of treating a disease caused by or associated with a mutation at position 12 or 13 in human RAS protein.

19. The molecule or nucleic acid for use according to claim 18, wherein the disease is a neoplastic disease, particularly cancer.

20. The molecule or nucleic acid for use according to claim 18 or 19, wherein the disease is pancreatic ductal adenocarcinoma, colorectal adenocarcinoma, multiple myeloma, lung  
5 adenocarcinoma, skin cutaneous melanoma, uterine corpus endometrioid carcinoma, uterine carcinosarcoma, thyroid carcinoma, acute myeloid leukaemia, bladder urothelial carcinoma, gastric adenocarcinoma, cervical adenocarcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer (NSCLC), or colorectal cancer.

21. A pharmaceutical composition comprising

10 the molecule according to any one of claims 1 to 16; or

a nucleic acid encoding the molecule according to any one of claims 1 to 16, wherein the molecule is a polypeptide.