

CLAIMS

1. A non-naturally occurring molecule configured to form an intermolecular beta-sheet with the β -aggregation prone region (APR) of the amino acid sequence GFLCVFAIN (SEQ ID NO: 3) in human RAS protein.
- 5 2. The molecule according to claim 1, wherein the RAS protein is KRAS, NRAS or HRAS protein, preferably KRAS protein.
3. The molecule according to claim 1 or 2, wherein the RAS protein is a mutant RAS protein, preferably a RAS protein mutated at position G12, G13 or Q61, more preferably at position G12.
4. The molecule according to claim 3, wherein the RAS protein is a G12V mutant RAS protein.
- 10 5. The molecule according to any one of claims 1 to 4, wherein the intermolecular beta-sheet involves at least 6 contiguous amino acids of the amino acid sequence GFLCVFAIN (SEQ ID NO: 3) in the human RAS protein.
6. The molecule according to claim 5, wherein the intermolecular beta-sheet involves the amino acid sequence LCVFAI (SEQ ID NO: 76) in the human RAS protein.
- 15 7. The molecule according to any one of claims 1 to 6, wherein the molecule is able to decrease the solubility or to induce the aggregation or inclusion body formation of the human RAS protein.
8. The molecule according to any one of claims 1 to 7, wherein the molecule comprises an amino acid stretch which participates in the intermolecular beta-sheet.
9. The molecule according to claim 8, wherein the amino acid stretch comprises at least 6
20 contiguous amino acids of the amino acid sequence GFLCVFAIN (SEQ ID NO: 3) or GFLSVFAIN (SEQ ID NO: 45).
10. The molecule according to claims 8 or 9, wherein the molecule comprises the amino acid stretch LSVFAI (SEQ ID NO: 6), FLSVFAI (SEQ ID NO: 46), GFLSVFAI (SEQ ID NO: 47), LSVFAIN (SEQ ID NO: 48), FLSVFAIN (SEQ ID NO: 49), or GFLSVFAIN (SEQ ID NO: 50).
- 25 11. The molecule according to any one of claims 8 to 10, wherein the molecule comprises the amino acid stretch LSVFAI (SEQ ID NO: 6).
12. The molecule according to any one of claims 8 to 11, wherein the amino acid stretch comprises one or more D-amino acids and/or analogues of one or more of its amino acids.
13. The molecule according to any one of claims 8 to 12, wherein the molecule comprises two or
30 more, preferably two, said amino acid stretches, which are identical or different.

14. The molecule according to any one of claims 8 to 13, 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.

15. The molecule according to any one of claims 8 to 14, wherein the molecule comprises, consists
5 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,

10 wherein:

P1 to P4 each independently denote an amino acid stretch as defined in any one of claims 8 to 12,

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
15 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
20 combinations thereof, and

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

16. The molecule according to claims 15, 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
25 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
30 between 1 and 5 units, wherein a unit is each independently an amino acid or PEG, such as wherein each linker is independently GS, PP, AS, SA, GF, FF, or GSGS (SEQ ID NO: 51), or D-isomers

and/or analogues thereof, preferably each linker is independently GS, PP or GSGS (SEQ ID NO: 51), preferably GS, or D-isomers and/or analogues thereof.

17. The molecule according to claim 15 or 16, wherein the molecule comprises, consists essentially of or consists of a peptide of the amino acid sequence KLSVFAIKGSKLSVFAIK (SEQ ID NO:7); 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.

18. The molecule according to any one of claims 1 to 17, 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.

19. The molecule according to any one of claims 1 to 18 for use in medicine; or

a nucleic acid encoding the molecule according to any one of claims 1 to 18, wherein the molecule is a polypeptide, for use in medicine.

20. The molecule according to any one of claims 1 to 18 for use in a method of treating a disease caused by or associated with a mutation in human RAS protein, preferably with a mutation at position 12 in human RAS protein, more preferably with G12V RAS mutation; or

a nucleic acid encoding the molecule according to any one of claims 1 to 18, wherein the molecule is a polypeptide, for use in a method of treating a disease caused by or associated with a mutation in human RAS protein, preferably with a mutation at position 12 in human RAS protein, more preferably with G12V RAS mutation.

21. The molecule or nucleic acid for use according to claim 20, wherein the disease is a neoplastic disease, particularly cancer.

22. The molecule or nucleic acid for use according to claim 20 or 21, wherein the disease is pancreatic ductal adenocarcinoma, colorectal adenocarcinoma, multiple myeloma, lung 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.

23. A pharmaceutical composition comprising

the molecule according to any one of claims 1 to 18; or

a nucleic acid encoding the molecule according to any one of claims 1 to 18, wherein the molecule is a polypeptide.