a) providing a water-in-oil emulsion comprising a plurality of aqueous microcapsules dispersed in the oil phase, wherein the aqueous phase comprises a library of genes encoding a repertoire of randomized peptides, components necessary to transcribe and translate the peptide genes, and p53wt genes, so that a plurality of aqueous microcapsules each comprise a peptide gene, components necessary to transcribe and translate the gene and a p53wt gene;

b) expressing the peptide genes and p53wt genes to produce their respective gene products within the microcapsules, wherein if the peptide gene encodes a peptide which restores the sequence-specific DNA binding of the p53wt then a p53wt /peptide/peptide gene complex forms;

c) breaking the emulsion; and

d) enriching for any p53/peptide/ peptide gene complexes.

[0018] In a twelfth aspect, there is provided a use of a peptide according to claim to any one of claims 1 to 14, an isolated nucleic acid molecule according to claim 15, a vector according to claim 16, or a pharmaceutical composition according to claim 17 or 18 in the manufacture of a medicament for the prophylaxis or treatment of a cancer associated with mutant p53 or a disorder characterized by an undesirably low level or a low activity of p53.

[0018a] In a thirteenth aspect, there is provided a peptide capable of restoring the sequence-specific DNA binding or transactivation function of a mutant p53, wherein the peptide:

(a) comprises a sequence selected from the group consisting of:

S P T T N H (SEQ ID NO:55)

M P H L M A C (SEQ ID NO:56)

T A L I D I W E H S V L G K G Y P R M S (SEQ ID NO:57)

I L N V L P L L A S R K P (SEQ ID NO:58)

VSWSACVLLELCNYFPENPIEEEDWACLG (SEQ ID NO:59)

R L Q Q V (SEQ ID NO:60)

V R H Q H V G A T I L G W K (SEQ ID NO:61)

V R H Q H V G A T I L G W KMGWTDH (SEQ ID NO:62)

MS P T T N H (SEQ ID NO:63)

MM P H L M A C (SEQ ID NO:64)

MT A L I D I W E H S V L G K G Y P R M S (SEQ ID NO:65)

MI L N V L P L L A S R K P (SEQ ID NO:66)

MVSWSACVLLELCNYFPENPIEEEDWACLG (SEQ ID NO:67)

MR L Q Q V (SEQ ID NO:68)

MV R H Q H V G A T I L G W K (SEQ ID NO:69)

MV R H Q H V G A T I L G W KMGWTDH (SEQ ID NO:70)

MLM

TTLIDIWEHSVLGKGYPRMS (SEQ ID NO:71)

M TTLIDIWEHSVLGKGYPRMS (SEQ ID NO:72)

RAVTDRPVPCPNPRLNLVAN (SEQ ID NO:73)

M RAVTDRPVPCPNPRLNLVAN (SEQ ID NO:74)

(b) is a variant of a peptide as defined in (a) above; or

(c) is a derivative of a peptide as defined in (a) or (b) above.

DEFINITIONS

[0019] The following are some definitions that may be helpful in understanding the description of the present invention. These are intended as general definitions and should in no way limit the scope of the present invention to those terms alone, but are put forth for a better understanding of the following description.

[0020] Unless the context requires otherwise or specifically stated to the contrary, integers, steps, or elements of the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

[0021] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated step or element or integer or group of steps or elements or integers, but not the exclusion of any other step or element or integer or group of elements or integers. Thus, in the context of this specification, the term “comprising” means “including principally, but not necessarily solely”.

[0022] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

Claims

1. A peptide capable of restoring the sequence-specific DNA binding or transactivation function of a mutant p53, wherein the peptide:

(a) comprises a sequence selected from the group consisting of:

S P T T N H (SEQ ID NO:55)

M P H L M A C (SEQ ID NO:56)

T A L I D I W E H S V L G K G Y P R M S (SEQ ID NO:57)

I L N V L P L L A S R K P (SEQ ID NO:58)

VSWSACVLLELCNYFPENPIEEEDWACLG (SEQ ID NO:59)

R L Q Q V (SEQ ID NO:60)

V R H Q H V G A T I L G W K (SEQ ID NO:61)

V R H Q H V G A T I L G W KMGWTDH (SEQ ID NO:62)

MS P T T N H (SEQ ID NO:63)

MM P H L M A C (SEQ ID NO:64)

MT A L I D I W E H S V L G K G Y P R M S (SEQ ID NO:65)

MI L N V L P L L A S R K P (SEQ ID NO:66)

MVSWSACVLLELCNYFPENPIEEEDWACLG (SEQ ID NO:67)

MR L Q Q V (SEQ ID NO:68)

MV R H Q H V G A T I L G W K (SEQ ID NO:69)

MV R H Q H V G A T I L G W KMGWTDH (SEQ ID NO:70)

MLM

TTLIDIWEHSVLGKGYPRMS (SEQ ID NO:71)

M TTLIDIWEHSVLGKGYPRMS (SEQ ID NO:72)

RAVTDRPVPCPNPRLNLVAN (SEQ ID NO:73)

M RAVTDRPVPCPNPRLNLVAN (SEQ ID NO:74)

(b) is a variant of a peptide as defined in (a) above; or

(c) is a derivative of a peptide as defined in (a) or (b) above.

2. The peptide which is a variant according to claim 1 (b), wherein the variant is a fragment of a peptide as defined in claim 1 (a).

3. The peptide which is a derivative according to claim 1 (c), wherein the derivative is a peptide which has undergone a post-translational modification.

4. The peptide according to claim 1 wherein the peptide is fused to a heterologous polypeptide sequence.

5. The peptide according to claim 1 wherein the peptide is a stably cross-linked peptide (a “stapled” peptide) wherein the cross-linked peptides contain at least two modified amino acids that together form an internal cross-link.

6. The peptide according to claim 1 wherein the mutant p53 is selected from the group consisting of: p53 G245S mutant, p53 R273H mutant p53 R248Q mutant the p53 R175H mutant.

7. An isolated nucleic acid molecule encoding a peptide according to claim 1.

8. A vector comprising an isolated nucleic acid molecule according to claim 7.

9. A pharmaceutical composition comprising a peptide according to claim 1, an isolated nucleic acid molecule according to claim 7, or a vector according to claim 8, wherein the pharmaceutical composition optionally comprises one or more pharmaceutically acceptable excipients, vehicles or carriers.

10. The pharmaceutical composition according to claim 9 wherein the pharmaceutical composition comprises a further therapeutic compound, for example an anti-cancer agent.

11. The peptide according to claim 1, an isolated nucleic acid molecule according to claim 7 or a vector according to claim 8 for use in medicine.

12. A method for obtaining a peptide which restores the sequence-specific DNA binding of a mutant p53 (mp53) the method comprising:

a) providing a water-in-oil emulsion comprising a plurality of aqueous microcapsules dispersed in the oil phase, wherein the aqueous phase comprises a library of genes encoding a repertoire of randomized peptides, components necessary to transcribe and translate the peptide genes, and mp53 genes, so that a plurality of aqueous microcapsules each comprise a peptide gene, components necessary to transcribe and translate the gene and a mp53 gene;

b) expressing the peptide genes and mp53 genes to produce their respective gene products within the microcapsules, wherein if the peptide gene encodes a peptide which restores the sequence-specific DNA binding of the mp53 then a mp53/peptide/peptide gene complex forms;

c) breaking the emulsion; and

d) enriching for any p53/peptide/peptide gene complexes.

13. The method according to claim 12 wherein the peptide genes comprise at least one response element (RE) to which mp53 having restored sequence-specific DNA binding can bind to.

14. The method according to claim 13 wherein the peptide genes comprise at least one response element (RE) to which mp53 having restored sequence-specific DNA binding can

bind to, a randomized reading frame, and regulatory elements which are operably linked to the reading frame to thereby enable its expression.

15. The method according to claim 12 wherein the peptide genes from the p53/peptide/peptide gene complexes are amplified prior to undergoing one or more further rounds of renewed encapsulation in aqueous microcapsules of a water-in-emulsion, expression of the peptide genes within the aqueous microcapsules and the formation of mp53/peptide/peptide gene complexes, breaking of the emulsion and enrichment for any p53/peptide/peptide gene complexes or amplification.

16. A method for obtaining a peptide which increases the sequence-specific DNA binding of a wild-type p53 (p53wt) the method comprising:

a) providing a water-in-oil emulsion comprising a plurality of aqueous microcapsules dispersed in the oil phase, wherein the aqueous phase comprises a library of genes encoding a repertoire of randomized peptides, components necessary to transcribe and translate the peptide genes, and p53wt genes, so that a plurality of aqueous microcapsules each comprise a peptide gene, components necessary to transcribe and translate the gene and a p53wt gene;

b) expressing the peptide genes and p53wt genes to produce their respective gene products within the microcapsules, wherein if the peptide gene encodes a peptide which restores the sequence-specific DNA binding of the p53wt then a p53wt/peptide/peptide gene complex forms;

c) breaking the emulsion; and

d) enriching for any p53/peptide/peptide gene complexes.

17. The method according to claim 16 wherein the peptide genes comprise at least one response element (RE) to which p53wt having increased sequence-specific DNA binding can bind to.

18. The method according to claim 17 wherein the peptide genes comprise at least one response element (RE) to which p53wt having increased sequence-specific DNA binding can bind to, a randomized reading frame, and regulatory elements which are operably linked to the reading frame to thereby enable its expression.

19. The method according to claim 16 wherein the peptide genes from the p53/peptide/peptide gene complexes are amplified prior to undergoing one or more further rounds of renewed encapsulation in aqueous microcapsules of a water-in-emulsion, expression of the peptide genes within the aqueous microcapsules and the formation of p53wt/peptide/peptide gene complexes, breaking of the emulsion and enrichment for any p53/peptide/peptide gene complexes or amplification.

20. Use of a peptide according to claim 1 or an isolated nucleic acid molecule according to claim 7 in the manufacture of a medicament for treating cancer or a disorder in a subject in need thereof, wherein the subject has cancer associated with a mutant p53 or a disorder characterized by a low level or a low activity of p53.