low affinity for Mdm2/Mdm4 (452 ± 11 nM and 646 ± 26 nM, respectively) and comes from a region of p53 that is known to interact with many other proteins.

[0006] Extensive studies have used phage display to select for linear peptides that bind Mdm2 with high affinity. However, the proline at position P12 is not observed in the electron density map in the crystal structure of the Mdm2: peptide complex and is not critical for binding to Mdm 2.

[0007] There is therefore a need to provide improved peptides or staple peptides that overcomes the disadvantages mentioned above to improve efficiency of binding to Mdm2/Mdm4 and reduce off target toxicity.

SUMMARY OF THE INVENTION

[0008] In a first aspect, the present invention is directed to a peptide comprising or consisting of the amino acid sequence of: TSFXaa$_1$EYW Xaa$_3$LLXaa$_2$ wherein Xaa$_1$ and Xaa$_2$ are any type of amino acid; and wherein Xaa$_3$ is N or A and wherein in case Xaa$_3$ is N, Xaa$_1$ is not A and/or Xaa$_2$ is not S. In a second aspect, the present invention is directed to a peptide comprising or consisting of the amino acid sequence of: TSFXaa$_1$EYWXaa$_3$LLXaa$_2$ wherein Xaa$_1$, Xaa$_2$ and Xaa$_3$ is independently any type of amino acid; and wherein the peptide is a crosslinked peptide with a cross-linker to connect a first amino acid Xaa$_1$ to a second amino acid Xaa$_2$. In a third aspect, the present invention is directed to a peptide comprising or consisting of the amino acid sequence of: TSFXaa$_1$EYWXaa$_3$LLXaa$_2$ Xaa$_4$ wherein Xaa$_1$, and Xaa$_2$ are independently any type of amino acid; wherein Xaa$_4$ is any type of amino acid other than P; wherein Xaa$_3$ is N or A and wherein in case Xaa$_3$ is N, Xaa$_1$ is not A and/or Xaa$_2$ is not S. In a fourth aspect, the present invention is directed to a use of the peptide according to the present invention or the isolated nucleic acid molecule according to the present invention or the vector according to the present invention in the manufacture of a medicament for treating or preventing cancer in a patient. According to ~~a first aspect~~one example, there is ~~provided~~described a peptide comprising or consisting of the amino acid sequence of:

TSFXaa$_1$EYW Xaa$_3$LLXaa$_2$

wherein Xaa$_1$ and Xaa$_2$ are any type of amino acid; and wherein Xaa$_3$ is N or A and wherein in case Xaa$_3$ is N, Xaa$_1$ is not A and/or Xaa$_2$ is not S.

[0009] According to ~~a second aspect~~another example, there is ~~provided~~described a peptide comprising or consisting of the amino acid sequence of:

$TSFXaa_1EYW\ Xaa_3LLXaa_2$

wherein Xaa_1, Xaa_2 and Xaa_3 is independently any type of amino acid; and

wherein the peptide is a crosslinked peptide with a cross-linker to connect a first amino acid Xaa_1 to a second amino acid Xaa_2.

[0010] According to ~~a third aspect~~one example, there is provided a peptide comprising or consisting of the amino acid sequence of:

$TSFXaa_1EYW\ Xaa_3LLXaa_2\ Xaa_4$

Wherein Xaa_1, Xaa_2 and Xaa_3 is independently any type of amino acid; and wherein Xaa_4 is any type of amino acid other than P.

[0011] According to ~~a fourth aspect~~another aspect, there is provided an isolated nucleic acid molecule encoding a peptide as described herein.

[0012] According to ~~a fifth aspect~~one aspect, there is provided a vector comprising an isolated nucleic acid molecule as described herein.

[0013] According to ~~a sixth aspect~~one aspect, there is provided a host cell comprising a nucleic acid molecule or a vector as described herein.

[0014] According to ~~a seventh aspect~~one aspect, there is provided a pharmaceutical composition comprising a peptide as described herein, an isolated nucleic acid molecule as described herein, or a vector as described herein.

[0015] According to ~~an eight aspect~~another example, there is provided the use of the peptide as described herein in the manufacture of a medicament for treating or preventing cancer.

[0016] According to ~~a ninth aspect~~another example, there is provided a method of treating or preventing cancer in a patient comprising administering a pharmaceutically effective amount of a peptide as described herein or an isolated nucleic acid molecule as described herein or a vector as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] The accompanying drawings illustrate a disclosed embodiment and serves to explain the principles of the disclosed embodiment. It is to be understood, however, that the drawings are designed for purposes of illustration only, and not as a definition of the limits of the invention.

[0018] **Fig. 1** is representative snapshot from simulations showing the crystal structure of SAH-8, MTide-01 and sMTide-01 in complex with Mdm2 and the biological activity of the peptides. **(a)** Crystal structure of SAH-8 in complex with Mdm2 (3V3B) showing the hydrocarbon staple interacting with the surface of the protein and the side-chain of T2 involved in helical capping hydrogen bond interactions with the backbone amide and side chain of N5. **(b)** A representative snapshot from a computer simulation of MTide-01 in complex with Mdm2 highlighting the hydrogen bond network around E5 and S2. S2 is involved in a weak hydrogen bond with the backbone amide of E5 and a much stronger hydrogen bond with the side chain of E5. In contrast to the wild type sequence E5 also interacts with the amide backbone of S2 further stabilizing the N-terminal of the bound helix resulting in optimal packing of the conserved F3 in the binding groove of Mdm2. **(c)** Overlay of representative snapshots from simulations of MTide-01 and sMTide-01 in complex with Mdm2 showing potential steric interference of N5 with the staple. The incorporation of the staple and the interactions it makes with the surface of Mdm2 causes the helix to roll. This orientates the staple into a position where it and the N5 side chain will modulate each other's

44. The pharmaceutical composition of claim 40, wherein the ATM inhibitors comprise inhibitors selected from the group consisting of:
2-Morpholin-4-yl-6-thianthren-1-yl-pyran-4-one (KU-55933);
(2R,6S)-2,6-Dimethyl-N-[5-[6-(4-morpholinyl)-4-oxo-4H-pyran-2-yl]-9H-thioxanthen-2-yl]-4-morpholineacetamide (KU-60019);
1-(6,7-Dimethoxy-4-quinazolinyl)-3-(2-pyridinyl)-1H-1,2,4-triazol-5-amine (CP466722);
α-Phenyl-N-[2,2,2-trichloro-1-[[[(4-fluoro-3-nitrophenyl)amino]thioxomethyl]amino] ethyl]benzene acetamide (CGK 733) and pharmaceutically acceptable salts thereof.

45. Use of the peptide according to any one of claims 1 to 32 or the isolated nucleic acid molecule according to claim 33, or the vector according to claim 34 in the manufacture of a medicament for treating or preventing cancer in a patient.

46. The use according to claim 45, wherein cancer comprises a tumor comprising a non-mutant p53 sequence.

47. The use according to claim 46 or 47, wherein cancer is selected from a group comprising or consisting of gastric cancer, colon cancer, lung cancer, breast cancer, bladder cancer, neuroblastoma, melanoma, and leukemia.

~~48. Method of treating or preventing cancer in a patient comprising administering a pharmaceutically effective amount of the peptide of any one of claims 1 to 32 or the isolated nucleic acid molecule according to claim 33, or the vector according to claim 34.~~

~~49.~~48. The ~~method~~ use according to ~~claim~~ any one of claims ~~48~~ 45 to 47 wherein ~~the method comprises the administration of~~ one or more further therapeutic agent(s) is/are to be administered to the patient, wherein said one or more further therapeutic agent(s) is/are to be administered ~~administration is~~ simultaneous, sequential or separate.

~~50. The method of claim 48 or 49, wherein administration of the peptide induces a reversible cell cycle arrest in non-cancerous proliferating cells.~~

~~51.~~49. The ~~method~~ use of any one of claims ~~48–~~45 to ~~50~~48, wherein the patient suffering or suspected to suffer~~ing~~ from cancer comprises a tumor with p53 deficient tumor cells or p53 genes comprising a mutation which causes the cancer.