WHAT IS CLAIMED:

1. A p53 peptidomimetic macrocycle, comprising:

(a) an i, i + 4 olefin staple and a polypeptide tail covalently linked at its N-terminus to the C-terminal amino acid of the p53 peptidomimetic macrocycle;

(b) an i, i+7 olefin staple and a polypeptide tail covalently linked at its N-terminus to the C-terminal amino acid of the p53 peptidomimetic macrocycle; or

(c) an i, i+7 di-alkyne staple and optionally a polypeptide tail covalently linked at its N-terminus to the C-terminal amino acid of the p53 peptidomimetic macrocycle,

wherein the p53 peptidomimetic macrocycle comprises all D-configuration amino acids and the polypeptide tail comprises three to nine amino acids, each amino acid of the polypeptide tail independently having a D-configuration or an L-configuration, or each amino acid in the polypeptide tail having a D-configuration.

2. The p53 peptidomimetic macrocycle of claim 1, wherein the p53 peptidomimetic macrocycle comprises an i, i+7 di-alkyne staple and a polypeptide tail covalently linked at its N-terminus to the C-terminal amino acid of the p53 peptidomimetic macrocycle.

3. The p53 peptidomimetic macrocycle of claim 1, wherein the p53 peptidomimetic macrocycle comprises 12 amino acids and an i, i + 4 olefin staple formed between the α-carbons of two α,α-disubstituted amino acids located at amino acid positions 6 and 10 of the p53 peptidomimetic macrocycle and a polypeptide tail covalently linked at its N-terminus to the C-terminal amino acid of the p53 peptidomimetic macrocycle, wherein the p53 peptidomimetic macrocycle comprises all D-configuration amino acids and the polypeptide tail comprises three to nine amino acids, each amino acid of the polypeptide tail independently having a D-configuration or an L-configuration or, in specific embodiments, each amino acid in the polypeptide tail having a D-configuration.

4. The p53 peptidomimetic macrocycle of claim 3, wherein the α,α-disubstituted amino acids at amino acid positions 6 and 10 of the p53 peptidomimetic macrocycle comprise (R)-2-amino-2-methylhept-6-enoic acid.

5. The p53 peptidomimetic macrocycle of claim 4, wherein the p53 peptidomimetic macrocycle further comprises D-6-fluoro-tryptophane at amino acid position 3 and D-p-CF_3-phenylalanine at amino acid position 7.

6. The p53 peptidomimetic macrocycle of claim 5, wherein the p53 peptidomimetic macrocycle further comprises threonine at amino acid position 1, alanine at amino acid position 2, tyrosine at amino acid position 4, alanine at amino acid position 5, glutamic acid at amino acid position 8, lysine or glutamine at amino acid position 9, leucine at amino acid position 11, and arginine or serine at amino acid position 12.

7. The p53 peptidomimetic macrocycle of claim 6, wherein the p53 peptidomimetic macrocycle comprises glutamine at amino acid at position 9 and serine at amino acid at position 12.

8. The p53 peptidomimetic macrocycle of claim 1, wherein the p53 peptidomimetic macrocycle comprises 12 amino acids and an i, i +7 di-alkyne staple formed between the α-carbons of two α,α-disubstituted amino acids located at amino acid positions 5 and 12 of the p53 peptidomimetic macrocycle, and optionally a polypeptide tail covalently linked at its N-terminus to the C-terminal amino acid of the p53 peptidomimetic macrocycle, wherein the p53 peptidomimetic macrocycle comprises all D-configuration amino acids and the polypeptide tail comprises three to nine amino acids, each amino acid of the polypeptide tail independently having a D-configuration or an L-configuration.

9. The p53 peptidomimetic macrocycle of claim 8, wherein the α,α-disubstituted amino acid at amino acid position 5 of the p53 peptidomimetic macrocycle comprises (S)-2-amino-2-methylhept-6-ynoic acid and the α,α-disubstituted amino acid at amino acid position 12 of the p53 peptidomimetic macrocycle comprises (R)-2-amino-2-methyloct-7-ynoic acid.

10. The p53 peptidomimetic macrocycle of claim 9, wherein the p53 peptidomimetic macrocycle further comprises D-6-fluoro-tryptophane at amino acid position 3 of the p53 peptidomimetic macrocycle and D-p-CF_3-phenylalanine at amino acid position 7 of the p53 peptidomimetic macrocycle.

11. The p53 peptidomimetic macrocycle of claim 10, wherein the p53 peptidomimetic macrocycle further comprises threonine at amino acid at position 1, alanine at amino acid position 2, tyrosine at amino acid position 4, asparagine at amino acid position 6, glutamic acid at amino acid position 8, lysine or glutamine at amino acid position 9, leucine at amino acid position 10, and leucine at amino acid position 11.

12. The p53 peptidomimetic macrocycle of claim 11, wherein the p53 peptidomimetic macrocycle comprises glutamine at amino acid position 9.

13. The p53 peptidomimetic macrocycle of claim 1, wherein the p53 peptidomimetic macrocycle comprises 12 amino acids and an i, i +7 olefin staple formed between the α-carbons of two α,α-disubstituted amino acids located at amino acid positions 5 and 12 of the p53 peptidomimetic macrocycle, and optionally a polypeptide tail, wherein the p53 peptidomimetic macrocycle comprises all D-configuration amino acids and the polypeptide tail comprises three to nine amino acids, each amino acid of the polypeptide tail independently having a D-configuration or an L-configuration.

14. The p53 peptidomimetic macrocycle of claim 13, wherein the α,α-disubstituted amino acid at amino acid position 5 of the p53 peptidomimetic macrocycle comprises (S)-2-amino-2-methyldec-9-enoic acid and the α,α-disubstituted amino acid at amino acid position 12 of the p53 peptidomimetic macrocycle comprises (R)-2-amino-2-methylhept-6-enoic acid.

15. The p53 peptidomimetic macrocycle of claim 14, wherein the p53 peptidomimetic macrocycle further comprises D-6-fluoro-tryptophane at amino acid position 3 of the p53 peptidomimetic macrocycle and D-p-CF_3-phenylalanine at amino acid position 7 of the p53 peptidomimetic macrocycle.

16. The p53 peptidomimetic macrocycle of claim 15, wherein the p53 peptidomimetic macrocycle further comprises threonine at amino acid at position 1, alanine at amino acid position 2, tyrosine at amino acid position 4, asparagine at amino acid

position 6, glutamic acid at amino acid position 8, lysine or glutamine at amino acid position 9, leucine at amino acid position 10, and leucine at amino acid position 11.

17. The p53 peptidomimetic macrocycle of claim 16, wherein the p53 peptidomimetic macrocycle comprises glutamine at amino acid position 9.

18. The p53 peptidomimetic macrocycle of claim 1 or 2, wherein the polypeptide tail comprises three to nine amino acids, each amino acid of the polypeptide tail independently having a D-configuration or an L-configuration, or each amino acid in the polypeptide tail having a D-configuration.

19. The p53 peptidomimetic macrocycle of claim 1 or 2, wherein the polypeptide tail comprises three to nine amino acids, each amino acid in the polypeptide tail having a D-configuration.

20. The p53 peptidomimetic macrocycle of claim 1 or 2, wherein the polypeptide tail comprises six amino acids, each amino acid of the polypeptide tail independently having a D-configuration or an L-configuration, or each amino acid in the polypeptide tail having a D-configuration.

21. The p53 peptidomimetic macrocycle of claim 1 or 2, wherein the polypeptide tail comprises an amino acid sequence set forth in SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23.

22. A p53 peptidomimetic macrocycle comprising:

$TAX^3YAX^6X^7EKX^{10}X^{11}X^{12}X^{13}X^{14}X^{15}X^{16}X^{17}X^{18}$-$X^{19}X^{20}X^{21}$ (SEQ ID NO: 17)

wherein X^3 is D-Trp, D-6-Fluoro-Trp, D-6-Chloro-Trp, D-6-Bromo-Trp, D-6-Iodo-Trp, D-6-methyl-Trp, D-6-cyano-Trp, D-6-hydroxy-Trp, D-6-NO_2-Trp, D-7-Fluoro-Trp, D-7-Chloro-Trp, D-7-Bromo-Trp, D-7-Iodo-Trp, D-7-methyl-Trp, D-7-cyano-Trp, D-7-hydroxy-Trp, D-7-NO_2-Trp, D-6,7-Fluoro-Trp, D-6,7-Chloro-Trp, D-6,7-Bromo-Trp, D-6,7-Iodo-Trp, D-6,7-methyl-Trp, D-6,7-cyano-Trp, D-6,7-hydroxy-Trp, or D-6,7-NO_2-Trp; X^6 is (R)-2-amino-2-methylhept-6-

enoic acid; X^7 is D-p-Fluoro-Phe, D-p-Chloro-Phe, D-p-Bromo-Phe, D-p-Iodo-Phe, D-p-methyl-Phe, D-p-cyano-Phe, D-p-hydroxy-Phe, D-p-NO_2-Phe, or D-p-CF_3-Phe; X^{10} is (R)-2-amino-2-methylhept-6-enoic acid; X^{11} is D-Leu; X^{12} is D-Arg or D-Ser; X^{13} is D-Ala, D-Glu, or D-Gla (γ-carboxylic glutamic acid); X^{14} is D-Ala; X^{15} is D-Ala, D-Phe, or D-Glu; X^{16} is D-Ala or absent; X^{17} is D-Ala, D-α-methyl-Glu, or absent; X^{18} is D-Ala or absent; X^{19} is an D-Ala or absent; X^{20} is D-Ala or absent; X^{21} is D-Ala or absent; the N-terminal amino group is optionally conjugated to an acyl group having the formula RCO-; R is an alkane having the formula C_nH_{2n+1}; n is an integer from 1 to 10; the C-terminal amino acid optionally comprises an amino group; amino acids 1-21 are D amino acids; and the staple is an olefin obtained through ring-closing metathesis between X^6 and X^{10}.

23. The p53 peptidomimetic macrocycle of claim 22, wherein X^3 is D-6-Fluoro-Trp; or wherein X^7 is D-p-CF_3-Phe; or wherein X^3 is D-6-Fluoro-Trp and X^7 is D-p-CF_3-Phe.

24. The p53 peptidomimetic macrocycle of claim 22, wherein the acyl group is an acetyl group.

25. A p53 peptidomimetic macrocycle comprising:

$TAX^3YX^5NX^7EX^9LX^{11}X^{12}X^{13}X^{14}X^{15}X^{16}X^{17}X^{18}$-$X^{19}X^{20}X^{21}$ (SEQ ID NO: 18)

wherein X^3 is D-Trp, D-6-Fluoro-Trp, D-6-Chloro-Trp, D-6-Bromo-Trp, D-6-Iodo-Trp, D-6-methyl-Trp, D-6-cyano-Trp, D-6-hydroxy-Trp, D-6-NO_2-Trp, D-7-Fluoro-Trp, D-7-Chloro-Trp, D-7-Bromo-Trp, D-7-Iodo-Trp, D-7-methyl-Trp, D-7-cyano-Trp, D-7-hydroxy-Trp, D-7-NO_2-Trp, D-6,7-Fluoro-Trp, D-6,7-Chloro-Trp, D-6,7-Bromo-Trp, D-6,7-Iodo-Trp, D-6,7-methyl-Trp, D-6,7-cyano-Trp, D-6,7-hydroxy-Trp, or D-6,7-NO_2-Trp; X^5 is (S)-2-amino-2-methylhept-6-ynoic acid; X^7 is D-p-Fluoro-Phe, D-p-Chloro-Phe, D-p-Bromo-Phe, D-p-Iodo-Phe, D-p-methyl-Phe, D-p-cyano-Phe, D-p-hydroxy-Phe, D-p-NO_2-Phe, or D-p-CF_3-Phe; X^9 is D-Lys or D-Gln; X^{11} is D-Leu; X^{12} is (R)-2-amino-2-methyloct-7-ynoic acid; X^{13} is D-Ala, D-Glu, D-Gla (γ-carboxylic glutamic acid) or absent; X^{14} is D-Ala or absent; X^{15} is D-Ala, D-Phe, or D-Glu or absent; X^{16} is D-Ala or absent; X^{17} is D-Ala, D-α-methyl-Glu, or absent; X^{18} is D-Ala or absent;

X^{19} is D-Ala or absent; X^{20} is D-Ala or absent; X^{21} is D-Ala or absent; the N-terminus is optionally conjugated to an acyl group having the formula RCO-; R is an alkane having the formula C_nH_{2n+1}; n is an integer from 1 to 10; the C-terminal amino acid optionally comprises an amino group; amino acids 1-21 are D amino acids; and the staple is a di-alkyne obtained through alkyne cross-coupling between X^5 and X^{12}.

26. The p53 peptidomimetic macrocycle of claim 25, wherein X^9 is D-Gln.

27. The p53 peptidomimetic macrocycle of claim 25, wherein X^3 is D-6-Fluoro-Trp; or wherein X^7 is D-p-CF_3-Phe; or wherein X^3 is D-6-Fluoro-Trp and X^7 is D-p-CF_3-Phe.

28. The p53 peptidomimetic macrocycle of claim 25, wherein the acyl group is an acetyl group.

29. A p53 peptidomimetic macrocycle comprising:

$TAX^3YX^5NX^7EX^9LX^{11}X^{12}X^{13}X^{14}X^{15}X^{16}X^{17}X^1X^{19}X^{20}X^{21}$ (SEQ ID NO: 27)

wherein X^3 is D-Trp, D-6-Fluoro-Trp, D-6-Chloro-Trp, D-6-Bromo-Trp, D-6-Iodo-Trp, D-6-methyl-Trp, D-6-cyano-Trp, D-6-hydroxy-Trp, D-6-NO_2-Trp, D-7-Fluoro-Trp, D-7-Chloro-Trp, D-7-Bromo-Trp, D-7-Iodo-Trp, D-7-methyl-Trp, D-7-cyano-Trp, D-7-hydroxy-Trp, D-7-NO_2-Trp, D-6,7-Fluoro-Trp, D-6,7-Chloro-Trp, D-6,7-Bromo-Trp, D-6,7-Iodo-Trp, D-6,7-methyl-Trp, D-6,7-cyano-Trp, D-6,7-hydroxy-Trp, or D-6,7-NO_2-Trp; X^5 is (S)-2-amino-2-methyldec-9-enoic acid; X^7 is D-p-Fluoro-Phe, D-p-Chloro-Phe, D-p-Bromo-Phe, D-p-Iodo-Phe, D-p-methyl-Phe, D-p-cyano-Phe, D-p-hydroxy-Phe, D-p-NO_2-Phe, or D-p-CF_3-Phe; X^9 is D-Lys or D-Gln; X^{11} is D-Leu; X^{12} is (R)-2-amino-2-methylhept-6-enoic acid; X^{13} is D-Ala, D-Glu, D-Gla (γ-carboxylic glutamic acid); X^{14} is D-Ala; X^{15} is D-Ala, D-Phe, D-Glu; X^{16} is D-Ala; X^{17} is D-Ala, D-α-methyl-Glu; X^{18} is D-Ala; X^{19} is D-Ala or absent; X^{20} is D-Ala or absent; X^{21} is D-Ala or absent; the N-terminus is optionally conjugated to an acyl group having the formula RCO-; R is an alkane having the formula C_nH_{2n+1}; n is an integer from 1 to 10; the C-terminal amino acid

optionally comprises an amino group; amino acids 1-21 are D amino acids; and the staple is an olefin obtained through ring-closing metathesis between X^5 and X^{12}.

30. The p53 peptidomimetic macrocycle of claim 29, wherein X^9 is D-Gln.

31. The p53 peptidomimetic macrocycle of claim 29, wherein X^3 is D-6-Fluoro-Trp; or wherein X^7 is D-p-CF_3-Phe; or wherein X^3 is D-6-Fluoro-Trp and X^7 is D-p-CF_3-Phe.

32. The p53 peptidomimetic macrocycle of claim 29, wherein the acyl group is an acetyl group.

33. A p53 peptidomimetic macrocycle comprising:

$TAX^3YX^5NX^7EX^9LX^{11}X^{12}$ (SEQ ID NO: 19)

wherein X^3 is D-Trp, D-6-Fluoro-Trp, D-6-Chloro-Trp, D-6-Bromo-Trp, D-6-Iodo-Trp, D-6-methyl-Trp, D-6-cyano-Trp, D-6-hydroxy-Trp, D-6-NO_2-Trp, D-7-Fluoro-Trp, D-7-Chloro-Trp, D-7-Bromo-Trp, D-7-Iodo-Trp, D-7-methyl-Trp, D-7-cyano-Trp, D-7-hydroxy-Trp, D-7-NO_2-Trp, D-6,7-Fluoro-Trp, D-6,7-Chloro-Trp, D-6,7-Bromo-Trp, D-6,7-Iodo-Trp, D-6,7-methyl-Trp, D-6,7-cyano-Trp, D-6,7-hydroxy-Trp, or D-6,7-NO_2-Trp; X^5 is (S)-2-amino-2-methylhept-6-ynoic acid; X^7 is D-p-Fluoro-Phe, D-p-Chloro-Phe, D-p-Bromo-Phe, D-p-Iodo-Phe, D-p-methyl-Phe, D-p-cyano-Phe, D-p-hydroxy-Phe, D-p-NO_2-Phe, or D-p-CF_3-Phe; X^9 is D-Lys or D-Gln; X^{11} is D-Leu; X^{12} is (R)-2-amino-2-methyloct-7-ynoic acid; the N-terminus is optionally conjugated to an acyl group having the formula RCO-; R is an alkane having the formula C_nH_{2n+1}; n is an integer from 1 to 10; the C-terminal amino acid optionally comprises an amino group; amino acids 1-12 are D amino acids; and the staple is a di-alkyne obtained through alkyne cross-coupling between X^5 and X^{12}.

34. The p53 peptidomimetic macrocycle of claim 33, wherein X^9 is D-Gln.

35. The p53 peptidomimetic macrocycle of claim 33, wherein X^3 is D-6-Fluoro-Trp; or wherein X^7 is D-p-CF_3-Phe; or wherein X^3 is D-6-Fluoro-Trp and X^7 is D-p-CF_3-Phe.

36. The p53 peptidomimetic macrocycle of claim 33, wherein the acyl group is an acetyl group.

37. A p53 peptidomimetic macrocycle comprising an amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 9, or SEQ ID NO: 10.

38. The p53 peptidomimetic macrocycle of claim 37, wherein p53 peptidomimetic macrocycle comprises an amino acid sequence set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 9.

39. A composition comprising the p53 peptidomimetic macrocycle of any one of claims 1-37 and a pharmaceutically acceptable carrier.

40. Use of the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 in the preparation of a medicament for treating cancer.

41. The p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 for use in the treatment of cancer.

42. The use of claim 40 or the p53 peptidomimetic macrocycle or composition for use of claim 41, wherein the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, head and neck cancer, urothelial cancer, breast cancer, gastrointestinal cancer, multiple myeloma, hepatocellular cancer, non-Hodgkin lymphoma, renal cancer, Hodgkin lymphoma, mesothelioma, ovarian cancer, small cell lung cancer, esophageal cancer, anal cancer, biliary tract cancer, colorectal cancer, cervical cancer, thyroid cancer, salivary cancer, pancreatic cancer, bronchus cancer, prostate cancer, pancreatic cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver

cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, and cancer of hematological tissues.

43. An *in vitro* method of modulating the activity of p53 and/or MDM2 and/or MDMX in a subject comprising administering to the subject the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39.

44. The p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 for use in modulating the activity of p53 and/or MDM2 and/or MDMX.

45. An *in vitro* method of antagonizing the interaction between p53 and MDM2 and/or between p53 and MDMX in a subject comprising administering to the subject the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39.

46. The p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 for use in antagonizing the interaction between p53 and MDM2 and/or between p53 and MDMX.

47. Use of the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 in the preparation of a medicament in combination with a chemotherapy agent or radiation for treating cancer in a subject.

48. The use of claim 47, wherein the chemotherapy agent or radiation is to be administered to the subject to be followed by administration of the p53 peptidomimetic macrocycle; the p53 peptidomimetic macrocycle is to be administered to the subject to be followed by administration of the chemotherapy agent or radiation; or the chemotherapy agent or radiation is to be administered to the subject simultaneously with the p53 peptidomimetic macrocycle.

49. A combination therapy for use in the treatment of cancer comprising the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 and a chemotherapy agent or radiation.

50. The combination therapy for use of claim 49, wherein the chemotherapy agent is selected from the group consisting of actinomycin, all-trans retinoic acid, alitretinoin, azacitidine, azathioprine, bexarotene, bleomycin, bortezomib, carmofur, carboplatin, capecitabine, cisplatin, chlorambucil, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, epothilone, etoposide, fluorouracil, gemcitabin, hydroxyurea, idarubicin, imatinib, ixabepilone, irinotecan, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, nitrosoureas, oxaliplatin, paclitaxel, pemetrexed, romidepsin, tegafur, temozolomide (oral dacarbazine), teniposide, tioguanine, topotecan, utidelone, valrubicin, vemurafenib, vinblastine, vincristine, vindesine, vinorelbine, and vorinostat.

51. Use of the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 in the preparation of a medicament in combination with a checkpoint inhibitor for treating cancer.

52. A combination therapy for use in the treatment of cancer comprising the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 and a checkpoint inhibitor.

53. The use of claim 51 or the combination therapy of claim 52, wherein the checkpoint inhibitor is an anti-PD1 antibody or an anti-PD-L1 antibody.

54. Use of the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 in the preparation of a medicament in combination with a vector comprising a nucleic acid molecule encoding a wild-type p53 or p53 variant or analog with transcriptional activation activity for treating cancer in a subject.

55. A combination therapy for use in the treatment of cancer comprising the p53 peptidomimetic macrocycle of any one of claims 1-38 or the composition of claim 39 and a vector comprising a nucleic acid molecule encoding a wild-type p53 or p53 variant or analog with transcriptional activation activity.

56. The use of claim 54 or the combination therapy for use of claim 55, wherein the vector is a plasmid, a retrovirus, adenovirus, or adeno-associated virus.

57. The use of claim 54, wherein the subject is to be administered a chemotherapy or radiation treatment to be prior to administration of the vector to the subject or to be subsequent to administration of the vector to the subject.

58. The use of claim 54, wherein the subject is to be administered a checkpoint inhibitor.