CLAIMS

What is claimed is:

1. A fusion protein comprising from N-terminus to C-terminus, a demethylation domain, an XTEN linker, and a nuclease-deficient RNA-guided DNA endonuclease enzyme.

2. The fusion protein of claim 1, wherein the demethylation domain is a TET1 domain, a TET2 domain, a TET3 domain, or a combination of two or more thereof.

3. The fusion protein of claim 2, wherein the demethylation domain is a TET1 domain.

4. The fusion protein of claim 2, wherein the TET1 domain comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:86, or SEQ ID NO:97.

5. The fusion protein of claim 1, wherein the nuclease-deficient RNA-guided DNA endonuclease enzyme is dCas9, dCas12a, dCpf1, Cas-phi, a helix-turn-helix motif, a helix-loop-helix domain, an HMB-box domain, a Wor3 domain, an OB-fold domain, an immunoglobulin domain, or a B3 domain.

6. The fusion protein of claim 5, wherein the nuclease-deficient RNA-guided DNA endonuclease enzyme is dCas9.

7. The fusion protein of claim 1, wherein the XTEN linker comprises from about 10 amino acid residues to about 864 amino acid residues.

8. The fusion protein of claim 7, wherein the XTEN linker comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:98.

9. The fusion protein of claim 1, wherein the fusion protein further comprises an epitope tag, a 2A peptide, a fluorescent protein tag, a nuclear localization signal peptide, or a combination of two or more thereof.

10. A fusion protein comprising from N-terminus to C-terminus, an RNA-binding sequence, an XTEN linker, and at least one transcriptional activator.

11. The fusion protein of claim 10, wherein the transcriptional activator is VP64,

p65, Rta, or a combination of two or more thereof.

12. The fusion protein of claim 11, wherein p65 comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:100.

13. The fusion protein of claim 11, wherein Rta comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:15 or SEQ ID NO:16.

14. The fusion protein of claim 11, wherein VP64 comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:17 or SEQ ID NO:18.

15. The fusion protein of claim 10, wherein the RNA-binding sequence is an MS2 RNA-binding sequence.

16. The fusion protein of claim 15, wherein the MS2 RNA-binding sequence comprises the amino acid sequence of SEQ ID NO:21.

17. The fusion protein of claim 10, wherein the XTEN linker comprises from about 10 amino acid residues to about 864 amino acid residues.

18. The fusion protein of claim 10 having an amino acid sequence with at least 90% sequence identity to SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, or SEQ ID NO:110.

19. The fusion protein of claim 10, wherein the fusion protein further comprises an epitope tag, a 2A peptide, a fluorescent protein tag, a nuclear localization signal peptide, or a combination of two or more thereof.

20. A fusion protein comprising from N-terminus to C-terminus, a demethylation domain, a first XTEN linker, a nuclease-deficient RNA-guided DNA endonuclease enzyme, a second XTEN linker, and a transcriptional activator.

21. The fusion protein of claim 20, wherein the transcriptional activator is VP64, p65, Rta, or a combination of two or more thereof.

22. A fusion protein comprising from N-terminus to C-terminus, a demethylation domain, an XTEN linker, and a nuclease-deficient RNA-guided DNA endonuclease enzyme.

23. The fusion protein of claim 20, further comprising a nuclear localization

sequence

24. The fusion protein of claim 20, wherein the demethylation domain is a TET1 domain, a TET2 domain, a TET3 domain, or a combination of two or more thereof.

25. The fusion protein of claim 24, wherein the demethylation domain is a TET1 domain.

26. The fusion protein of claim 20, wherein the nuclease-deficient RNA-guided DNA endonuclease enzyme is dCas9, dCas12a, dCpf1, Cas-phi, a leucine zipper domain, a winged helix domain, a helix-turn-helix motif, a helix-loop-helix domain, an HMB-box domain, a Wor3 domain, an OB-fold domain, an immunoglobulin domain, or a B3 domain.

27. The fusion protein of claim 26, wherein the nuclease-deficient RNA-guided DNA endonuclease enzyme is dCas9.

28. The fusion protein of claim 20, wherein the first XTEN linker and the second XTEN linker each independently comprise from about 10 amino acid residues to about 864 amino acid residues.

29. The fusion protein of claim 20, wherein the fusion protein further comprising an epitope tag, a 2A peptide, a fluorescent protein tag, or a combination of two or more thereof.

30. A fusion protein comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:111, SEQ ID NO:112, or SEQ ID NO:113.

31. The fusion protein of claim 30, comprising an amino acid sequence having at least 95% sequence identity to SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:111, SEQ ID NO:112, or SEQ ID NO:113.

32. The fusion protein of claim 31 comprising SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:111, SEQ ID NO:112, or SEQ ID NO:113.

33. A method of activating or reactivating a target nucleic acid sequence in a cell, the method comprising:

(i) delivering a first polynucleotide encoding a fusion protein of claim 1 to a cell containing the target nucleic acid; and

(ii) delivering to the cell a second polynucleotide comprising: (a) a sgRNA or (b) a

cr:tracrRNA;

thereby activating or reactivating the target nucleic acid sequence in the cell.

34. The method of claim 32, wherein the target nucleic acid sequence comprises a CpG island.

35. The method of claim 32, wherein the target nucleic acid sequence comprises a non-CpG island.

36. The method of claim 32, wherein the second polynucleotide comprises the sgRNA.

37. The method of claim 32, wherein the sgRNA comprises at least one MS2 stem loop.

38. The method of claim 37, wherein the sgRNA comprises two MS2 stem loops.

39. The method of claim 32, wherein the second polynucleotide encodes a transcriptional activator.

40. The method of claim 39, wherein the transcriptional activator is VP64, p65, Rta, or a combination of two or more thereof.

41. The method of claim 32, wherein the second polynucleotide further encodes an MS2 RNA-binding sequence.

42. The method of claim 41, wherein the MS2 RNA-binding sequence comprises the amino acid sequence of SEQ ID NO:21.

43. The method of claim 32, wherein the second polynucleotide further encodes for an XTEN linker, an epitope tag, a 2A peptide, a fluorescent protein tag, a nuclear localization signal peptide, or a combination of two or more thereof.

44. The method of claim 32, further comprising delivering to the cell a third polynucleotide encoding a second fusion protein which comprises a transcriptional activator.

45. The method of claim 44, wherein the transcriptional activator is VP64, p65, Rta, or a combination of two or more thereof.

46. The method of claim 44, wherein the second fusion protein further comprises an

MS2 RNA-binding sequence.

47. The method of claim 46, wherein the MS2 RNA-binding sequence comprises the amino acid sequence of SEQ ID NO:21.

48 . The method of claim 44, wherein the second fusion protein further comprises an XTEN linker, an epitope tag, a 2A peptide, a fluorescent protein tag, a nuclear localization signal peptide, or a combination of two or more thereof.

49. A fusion protein comprising from N-terminus to C-terminus, a demethylation domain, an XTEN linker, and a nuclease-deficient DNA endonuclease enzyme.

50. The fusion protein of claim 49, wherein the demethylation domain is a TET1 domain, a TET2 domain, a TET3 domain, or a combination of two or more thereof.

51. The fusion protein of claim 49, wherein the demethylation domain is a TET1 domain.

52. The fusion protein of claim 51, wherein the TET1 domain comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:86, or SEQ ID NO:97.

53. The fusion protein of claim 49, wherein the nuclease-deficient DNA endonuclease enzyme is a zinc finger domain.

54. The fusion protein of claim 49, wherein the nuclease-deficient DNA endonuclease enzyme is a TALE.

55. The fusion protein of claim 49, wherein the XTEN linker comprises from about 10 amino acid residues to about 864 amino acid residues.

56. The fusion protein of claim 55, wherein the XTEN linker comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:98.

57. The fusion protein of claim 49, wherein the fusion protein further comprises an epitope tag, a 2A peptide, a fluorescent protein tag, a nuclear localization signal peptide, or a combination of two or more thereof.

58. A fusion protein comprising from N-terminus to C-terminus, a demethylation domain, a first XTEN linker, a nuclease-deficient DNA endonuclease enzyme, a second XTEN linker, and a transcriptional activator.

59. The fusion protein of claim 58, wherein the transcriptional activator is VP64, p65, Rta, or a combination of two or more thereof.

60. A fusion protein comprising from N-terminus to C-terminus, a demethylation domain, an XTEN linker, and a nuclease-deficient DNA endonuclease enzyme.

61. The fusion protein of claim 58, further comprising a nuclear localization sequence.

62. The fusion protein of claim 58, wherein the demethylation domain is a TET1 domain, a TET2 domain, a TET3 domain, or a combination of two or more thereof.

63. The fusion protein of claim 62, wherein the demethylation domain is a TET1 domain.

64. The fusion protein of claim 58, wherein the nuclease-deficient DNA endonuclease enzyme is a zinc finger domain.

65. The fusion protein of claim 58, wherein the nuclease-deficient DNA endonuclease enzyme is a TALE.

66. The fusion protein of claim 58, wherein the first XTEN linker and the second XTEN linker each independently comprise from about 10 amino acid residues to about 864 amino acid residues.

67. The fusion protein of claim 58, wherein the fusion protein further comprising an epitope tag, a 2A peptide, a fluorescent protein tag, or a combination of two or more thereof.

68. A method of activating or reactivating a target nucleic acid sequence in a cell, the method comprising delivering a polynucleotide encoding a fusion protein of claim 58 to a cell containing the target nucleic acid; thereby activating or reactivating the target nucleic acid sequence in the cell.

69. The method of claim 68, wherein the transcriptional activator is VP64, p65, Rta, or a combination of two or more thereof.