

WHAT IS CLAIMED IS:

1. A composition comprising: (a) a programmable DNA modification protein or nucleic acid encoding the programmable DNA modification protein; and (b) at least one programmable DNA binding protein or nucleic acid encoding the at least one programmable DNA binding protein.
2. The composition of claim 1, wherein the programmable DNA modification protein is a RNA-guided clustered regularly interspersed short palindromic repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR/Cas) nuclease system, a CRISPR/Cas dual nickase system, a zinc finger nuclease (ZFN), a transcription activator-like effector nuclease (TALEN), a meganuclease, a fusion protein comprising a programmable DNA binding domain linked to a nuclease domain, or a fusion protein comprising a programmable DNA binding domain linked to a non-nuclease domain.
3. The composition of claim 2, wherein the programmable DNA binding domain of the fusion protein is a catalytically inactive CRISPR/Cas system, a catalytically inactive meganuclease, a zinc finger protein, or a transcription activator-like effector.
4. The composition of claims 2 or 3, wherein the non-nuclease domain of the fusion protein has acetyltransferase activity, deacetylase activity, methyltransferase activity, demethylase activity, kinase activity, phosphatase activity, ubiquitin ligase activity, deubiquitinating activity, adenylation activity, deadenylation activity, SUMOylating activity, deSUMOylating activity, ribosylation activity, deribosylation activity, myristoylation activity, demyristoylation activity, citrullination activity, helicase activity, amination activity, deamination activity, alkylation activity, dealkylation activity, oxidation activity, transcriptional activation activity, or transcriptional repressor activity.

5. The composition of claim 4, wherein the non-nuclease domain of the fusion protein has cytosine deaminase activity, histone acetyltransferase activity, transcriptional activation activity, or transcriptional repressor activity.
6. The composition of any one of claims 1 to 5, wherein the at least one programmable DNA binding protein is a catalytically inactive CRISPR/Cas protein, a catalytically inactive meganuclease, a zinc finger protein, a transcription activator-like effector, a CRISPR/Cas nickase, a ZFN nickase, a TALEN nickase, or a meganuclease nickase.
7. The composition of any one of claims 1 to 6, wherein nucleic acid encoding the programmable DNA modification protein and the at least one programmable DNA binding protein is RNA or DNA, and/or wherein said nucleic acid is part of a plasmid vector or a viral vector.
8. The composition of any one of claims 1 to 6, wherein the programmable DNA modification protein is a CRISPR/Cas nuclease system, a CRISPR/Cas dual nickase system, or catalytically inactive CRISPR/Cas system linked to a non-nuclease domain, and the at least one programmable DNA binding protein is a catalytically inactive CRISPR/Cas system, wherein each CRISPR/Cas system comprises a CRISPR/Cas protein and a guide RNA.
9. The composition of claim 8, wherein each CRISPR/Cas nuclease system is a type I CRISPR/Cas system, a type II CRISPR/Cas system, a type III CRISPR/Cas system, or a type V CRISPR/Cas system.
10. The composition of claim 9, wherein each CRISPR/Cas nuclease system is a type II CRISPR/Cas system or a type V CRISPR/Cas system.
11. The composition of any one of claims 8 to 10, wherein nucleic acid encoding each CRISPR/Cas protein is mRNA or DNA.

12. The composition of any one of claims 8 to 11, wherein nucleic acid encoding each CRISPR/Cas protein and/or nucleic acid encoding each guide RNA is part of a plasmid vector or a viral vector.
13. The composition of any one of claims 8 to 11, wherein the guide RNA of each CRISPR/Cas system is enzymatically synthesized.
14. The composition of any one of claims 8 to 11, wherein the guide RNA of each CRISPR/Cas system is at least partially chemically synthesized.
15. A kit comprising the composition of any one of claims 1 to 14.
16. A method for increasing targeted genome modification efficiency and/or specificity in a eukaryotic cell, the method comprising introducing into the eukaryotic cell:
 - (a) a programmable DNA modification protein or nucleic acid encoding the programmable DNA modification protein and;
 - (b) at least one programmable DNA binding protein or nucleic acid encoding the at least one programmable DNA binding protein;wherein the programmable DNA modification protein is targeted to a target chromosomal sequence and each of the at least one programmable DNA binding protein is targeted to a site proximal to the target chromosomal sequence, and binding of the at least one programmable DNA binding protein to the site proximal to the target chromosomal sequence increases accessibility of the programmable DNA modification protein to the target chromosomal sequence, thereby increasing targeted genome modification efficiency and/or specificity.
17. The method of claim 16, wherein the site proximal to the target chromosomal sequence is located within about 250 base pairs on either side of the target chromosomal sequence.

18. The method of claim 17, wherein the wherein the site proximal to the target chromosomal sequence is located within about 100 base pairs on either side of the target chromosomal sequence.
19. The method of claim 18, wherein the wherein the site proximal to the target chromosomal sequence is located within about 75 base pairs on either side of the target chromosomal sequence.
20. The method of claim 19, wherein the wherein the site proximal to the target chromosomal sequence is located within about 50 base pairs on either side of the target chromosomal sequence.
21. The method of claim 20, wherein the wherein the site proximal to the target chromosomal sequence is located within about 25 base pairs on either side of the target chromosomal sequence.
22. The method of any one of claims 16 to 21, wherein the programmable DNA modification protein is CRISPR/Cas nuclease system, a CRISPR/Cas dual nickase system, a zinc finger nuclease (ZFN), a transcription activator-like effector nuclease (TALEN), a meganuclease, a fusion protein comprising a programmable DNA binding domain linked to a nuclease domain, or a fusion protein comprising a programmable DNA binding domain linked to a non-nuclease domain.
23. The method of claim 22, wherein the programmable DNA binding domain of the fusion protein is a catalytically inactive CRISPR/Cas system, a catalytically inactive meganuclease, a zinc finger protein, or a transcription activator-like effector.
24. The method of claims 22 or 23, wherein the non-nuclease modification domain of the fusion protein has acetyltransferase activity, deacetylase activity, methyltransferase activity, demethylase activity, kinase activity, phosphatase activity, ubiquitin ligase activity, deubiquitinating activity,

adenylation activity, deadenylation activity, SUMOylating activity, deSUMOylating activity, ribosylation activity, deribosylation activity, myristoylation activity, demyristoylation activity, citrullination activity, helicase activity, amination activity, deamination activity, alkylation activity, dealkylation activity, oxidation activity, transcriptional activation activity, or transcriptional repressor activity.

25. The method of claim 24, wherein the non-nuclease domain of the fusion protein has cytosine deaminase activity, histone acetyltransferase activity, transcriptional activation activity, or transcriptional repressor activity.
26. The method of any one of claims 16 to 25, wherein the at least one programmable DNA binding protein is a catalytically inactive CRISPR/Cas system, a catalytically inactive meganuclease, a zinc finger protein, a transcription activator-like effector, a CRISPR/Cas nickase, a ZFN nickase, a TALEN nickase, or a meganuclease nickase.
27. The method of any one of claims 16 to 26, wherein the programmable DNA modification protein is a CRISPR/Cas nuclease system, a CRISPR/Cas dual nickase system, or catalytically inactive CRISPR/Cas system linked to a non-nuclease domain, and the at least one programmable DNA binding protein is a catalytically inactive CRISPR/Cas system, wherein each CRISPR/Cas system comprises a CRISPR/Cas protein and a guide RNA.
28. The method of claim 27, wherein the guide RNA of each CRISPR/Cas system is at least partially chemically synthesized.
29. The method of claim 27, wherein the guide RNA of each CRISPR/Cas system is enzymatically synthesized.
30. The method of any one of claims 16 to 29, wherein the eukaryotic cell is *in vitro*.

31. The method of any one of claims 16 to 29, wherein the eukaryotic cell is *in vivo*.
32. The method of any one of claims 16 to 31, wherein the eukaryotic cell is a mammalian cell.
33. The method of claim 32, wherein the mammalian cell is a human cell.
34. The method of claim 32, wherein the mammalian cell is a non-human cell.
35. A method for detecting a chromosomal sequence in a eukaryotic cell, the method comprising:
 - I. introducing into the eukaryotic cell (a) a programmable DNA binding protein comprising at least one detectable marker domain or nucleic acid encoding the programmable DNA binding protein comprising at least one detectable marker domain; and (b) at least one programmable DNA binding protein or nucleic acid encoding the at least one programmable DNA binding protein, wherein the programmable DNA binding protein comprising at least one detectable marker domain is targeted to a target chromosomal sequence and each of the at least one programmable DNA binding protein is targeted to a site proximal to the target chromosomal sequence, and binding of the at least one programmable DNA binding protein to the site proximal to the target chromosomal sequence increases accessibility of the programmable DNA binding protein comprising at least one detectable marker domain to the target chromosomal sequence; and
 - II. detecting the programmable DNA binding protein comprising at least one detectable marker domain bound to the target chromosomal sequence.
36. The method of claim 35, wherein the site proximal to the target chromosomal sequence is located within about 250 base pairs on either side of the target chromosomal sequence.

37. The method of claim 36, wherein the wherein the site proximal to the target chromosomal sequence is located within about 100 base pairs on either side of the target chromosomal sequence.
38. The method of claim 37, wherein the wherein the site proximal to the target chromosomal sequence is located within about 75 base pairs on either side of the target chromosomal sequence.
39. The method of claim 38, wherein the wherein the site proximal to the target chromosomal sequence is located within about 50 base pairs on either side of the target chromosomal sequence.
40. The method of claim 39, wherein the wherein the site proximal to the target chromosomal sequence is located within about 25 base pairs on either side of the target chromosomal sequence.
41. The method of any one of claims 35 to 40, wherein the at least one detectable marker domain of the programmable DNA binding protein comprising at least one detectable marker domain is a fluorescent protein, a fluorescent tag, an epitope tag, or a naturally occurring epitope within the programmable DNA binding protein.
42. The method of any one of claims 35 to 41, wherein the programmable DNA binding protein comprising at least one detectable marker domain is a catalytically inactive CRISPR/Cas system linked to at least one detectable marker domain, a catalytically inactive meganuclease linked to at least one detectable marker domain, a zinc finger protein linked to at least one detectable marker domain, or a transcription activator-like effector linked to at least one detectable marker domain.
43. The method of any one of claims 35 to 42, wherein the at least one programmable DNA binding protein is a catalytically inactive CRISPR/Cas system, a catalytically inactive meganuclease, a zinc finger protein, a

transcription activator-like effector, a CRISPR/Cas nickase, a ZFN nickase, a TALEN nickase, or a meganuclease nickase.

44. The method of any one of claims 35 to 43, wherein the programmable DNA binding protein comprising at least one detectable marker domain is a catalytically inactive CRISPR/Cas system linked to at least one detectable marker domain, and the at least one programmable DNA binding protein is a catalytically inactive CRISPR/Cas system, wherein each CRISPR/Cas system comprises a CRISPR/Cas protein and a guide RNA.
45. The method of claim 44, where the guide RNA of each CRISPR/Cas system is at least partially chemically synthesized.
46. The method of claim 44, where the guide RNA of each CRISPR/Cas system is enzymatically synthesized.
47. The method of any one of claims 35 to 46, wherein the eukaryotic cell is a mammalian cell.
48. The method of claim 47, wherein the mammalian cell is a human cell.
49. The method of claim 47, wherein the mammalian cell is a non-human cell.
50. The method of any one of claims 35 to 49, wherein the eukaryotic cell is live or fixed.
51. The method of any one of claims 35 to 50, wherein the detecting comprises dynamic live cell imaging, fluorescent microscopy, confocal microscopy, immunofluorescence, immunodetection, RNA-protein binding, or protein-protein binding.