

CLAIMS

What is claimed is:

1. A construct of Formula III:

5'-(A_{m1}-B_{m2})_{n1}-CasN-(A_{m3}-B_{m4})_{n2}-CasC-T_p-E-3' (III),

wherein:

one of A and B is a polynucleotide encoding DNMT3A; and the other of A and B is a polynucleotide encoding DNMT3L;

CasN is a polynucleotide encoding a N-terminal portion of dCas9;

CasC is a polynucleotide encoding a C-terminal portion of dCas9;

E is 5'-(A_{m5}-B_{m6})_{n3}-K_r-D_q-3';

K is a polynucleotide encoding KRAB;

D is a polynucleotide encoding a modulator of gene expression;

T comprises (a) a polynucleotide encoding an epitope capable of binding to an antibody or antigen binding fragment thereof, and further comprises (b) a polynucleotide encoding a self cleaving peptide at the 3' end of the polynucleotide in (a), and at the 3' end of the nucleotide encoding the self cleaving peptide in (b) further comprises (c) polynucleotide encoding an antibody or antigen binding fragment thereof that is capable of binding to the epitope;

m1, m2, m3, m4, m5, and m6 are each independently 1;

n2 is 0; n1 is 1 and n3 is 0; or n1 is 0 and n3 is 1;

p is 1;

q is 0;

r is 1.

2. The construct of claim 1, of Formula IIIb-1:

5'-(A-B)-CasN-CasC-T-K -3' (IIIb-1).

3. The construct of claim 1, of Formula IIIc-1:

5'-CasN-CasC-T-(A-B)-K -3' (IIIc-1).

4. The construct of claim 1, wherein the self cleaving peptide is T2A.

5. The construct of claim 1, wherein the DNMT3A comprises the amino acid sequence of SEQ ID NO: 69.
6. The construct of claim 5, wherein the polynucleotide encoding the DNMT3A comprises the nucleic acid sequence of SEQ ID NO: 83.
7. The construct of claim 1, wherein the DNMT3L comprises the amino acid sequence of any one of SEQ ID NOS: 74-82.
8. The construct of claim 7, wherein the polynucleotide encoding the DNMT3L comprises the nucleic acid sequence of any one of SEQ ID NOS: 84-92.
9. The construct of claim 1, wherein the KRAB comprises the amino acid sequence of SEQ ID NO: 51, 53, or 230-241.
10. The construct of claim 9, wherein the polynucleotide encoding the KRAB comprises the nucleic acid sequence of SEQ ID NO: 52, 54, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226 or 228.
11. The construct of claim 1, wherein the dCas9 comprises a *Staphylococcus pyogenes* dCas9.
12. The construct of claim 11, wherein the dCas9 comprises the amino acid sequence of SEQ ID NOS: 1.
13. The construct of claim 11, wherein the polynucleotide encoding the dCas9 comprises the nucleic acid sequence of SEQ ID NO: 26.
14. The construct of claim 1, wherein the epitope capable of binding to an antibody or an antigen binding fragment thereof is selected from a group consisting of GCN4, 10x GCN4.
15. The construct of claim 14, wherein the GCN4 comprises the amino acid sequence of SEQ ID NO: 97.

16. The construct of claim 15, wherein the polynucleotide encoding the GCN4 comprises the nucleic acid sequence of SEQ ID NO: 101.
17. The construct of claim 16, wherein the antibody or antigen binding fragment is a single domain antibody, a scFv, a Fab, a VH, a VHH or an antibody mimetic.
18. The construct of claim 17, wherein the antigen binding fragment is a scFv.
19. The construct of claim 1, comprising the nucleic acid sequence of any one of SEQ ID NOs: 162-189.
20. A polypeptide expressed by the construct of any one of claims 1-19.
21. A composition comprising the construct of any one of claims 1-19.