CLAIMS

1. A method for synthesizing a transcription activator-like effector (TALE) protein to target nucleic acid sequence comprising a chemically modified nucleic acid base, said method comprising assembling a plurality of TALE-like repeat sequences, each of said sequences comprising a repeat variable-diresidue (RVD) specific to each nucleic acid base of said sequence, wherein the RVD(s) that specifically targets the chemically modified nucleic acid base within said nucleic acid target sequence are selected from X* or ** , where X represents one amino acid residue selected from the group of A,G, V, L, I, M, S, T, C, P, D, E, F, Y, W, Q, N, H, R and K and * represents a gap in one position of the RVD.

2. The method according to claim 1 wherein said method comprises:

(a) determining a nucleic acid target sequence comprising chemically modified nucleic acid base in the genome of a cell;

(b) assembling TALE-like repeat polynucleotide sequences, each repeat being specific to each nucleic acid base of said nucleic acid target sequence by encoding a repeat variable-diresidue (RVD) comprising at least one RVD selected from the group consisting of:

- HD for recognizing C;
- NG for recognizing T;
- NI for recognizing A;
- NN for recognizing G or A;
- NS for recognizing A or C or G or T;
- HG for recognizing T;
- IG for recognizing T;
- NK for recognizing G;
- HA for recognizing C;
- ND for recognizing C;
- HI for recognizing C;
- HN for recognizing G;
- NA for recognizing G;
- SN for recognizing G or A; and
- YG for recognizing T;

wherein said RVD(s) specifically targeting the chemically modified nucleic acid base(s) in the nucleic acid target sequence are selected from the RVDs X* and **, where

- X represents one amino acid residue selected from the group of A, G, V, L, I, M, S, T, C, P, D, E, F, Y, W, Q, N, H, R and K, and

- * represents a gap in one position of the RVD,

(c) expressing said polynucleotide sequence assembled in step b) in said cell.

3. The method according to claim 1 or 2 wherein said RVD specifically targeting the chemically modified nucleic acid base(s) are preferentially selected from RVD N*, T*, Q* and H*.

4. The method according to claims 1 to 3 wherein said chemically modified nucleic acid base is a 5-methyl-cytosine.

5. A method to synthesize a chimeric protein to process nucleic acid at a locus defined by a nucleic acid target sequence that comprises a chemically modified base, said method comprising:

(a) synthesizing a polynucleotide sequence comprising a fusion of :

(i) a first polynucleotide encoding a transcription activator-like effector (TALE) protein comprising a plurality of TALE-like repeat sequences, each repeat comprising a repeat variable-diresidue (RVD) specific to each nucleic acid base of said nucleic acid target sequence, wherein the RVD(s) that specifically targets the chemically modified nucleic acid base within said nucleic acid target sequence are selected from X* or **, preferably N*, Q*, T* or H* where X represents one amino acid residue selected from the group of A,G, V, L, I, M, S, T, C, P, D, E, F, Y, W, Q, N, H, R and K and * represents a gap in one position of the RVD;

(ii) a second polynucleotide encoding an additional protein domain to process nucleic acid within or adjacent to said nucleic acid target sequence that comprises a chemically modified nucleic acid base;

(c) expressing said polynucleotide sequence of step a) into a host cell.

6. The method of claim 5 wherein said additional protein domain is an endonuclease.

7. A TALE-nuclease comprising amino acid sequence selected from the group consisting of SEQ ID NO: 38 to SEQ ID NO: 49.

8. A method to bind a nucleic acid target sequence comprising at least one chemically modified nucleic acid base, said method comprising contacting:
(i) a nucleic acid target sequence comprising chemically modified nucleic acid base and
(ii) a TALE protein comprising a repeat variable-diresidue (RVD) specific to each nucleic acid base of said nucleic acid target sequence, wherein the RVD(s) that specifically targets the chemically modified nucleic acid base within said nucleic acid target sequence are selected from X* or ** , preferably N*, Q*, T* or H* where X represents one amino acid residue selected from the group of A,G, V, L, I, M, S, T, C, P, D, E, F, Y, W, Q, N, H, R and K and * represents a gap in one position of the RVD.

9. A method to bind a nucleic acid target sequence comprising at least one chemically modified nucleic acid base, said method comprising:
(a) providing a cell containing a nucleic acid target sequence that comprises a chemically modified nucleic acid base,
(b) synthesizing within said cell a TALE protein according to claims 1 to 5 directed to said nucleic acid target sequence and,
(c) testing the binding affinity of said TALE protein with said nucleic acid target sequence that comprises said chemically modified nucleic acid base.

10. The method according to claim 8 or 9 wherein the said nucleic acid target sequence comprising at least one chemically modified dinucleotide selected from the group consisting of CpG, CpA, CpT, CpC.

11. A method to process a nucleic acid target sequence comprising at least one chemically modified nucleic acid base comprising:

(a) providing a cell containing a nucleic acid target sequence that comprises a chemically modified nucleic acid base;

(b) synthesizing within said cell a chimeric protein according to claims 5 to 6 directed to said nucleic acid sequence, so that said chimeric protein process the nucleic acid within or adjacent to said nucleic acid target sequence independently of chemical modification and,

(c) testing the nucleic acid processing at the locus of said nucleic acid target sequence.

12. The method according to claim 11 wherein said protein domain has a catalytical activity selected from the group consisting of nuclease activity, polymerase activity, kinase activity, phosphatase activity, methylase activity, topoisomerase activity, integrase activity, transposase activity, ligase activity, helicase activity, recombinase activity .

13. The method according to claim 11 wherein said additional protein domain is a transcription activator.

14. The method according to claim 11 wherein said nucleic acid target sequence is a methylated promoter sequence.

15. The method according to claim 11 wherein said additional protein domain is an endonuclease.

16. The method according to claim 15 further comprising providing to the cell an exogenous nucleic acid comprising a sequence homologous to at least a portion of the nucleic acid target sequence, such that homologous recombination occurs between the nucleic acid target sequence and the exogenous nucleic acid.

17. A method to detect at least one chemically modified nucleic acid base in a nucleic acid target sequence comprising:

(a) binding said nucleic acid target sequence with a transcription activator-like effector (TALE) protein comprising a plurality of TALE-like repeat sequences, each of said sequences comprising a repeat variable-diresidue (RVD) specific to each nucleic acid base of said nucleic acid target sequence wherein at least one RVD selected from the group consisting of:
   - HD for recognizing C;

- NG for recognizing T;
- NI for recognizing A;
- NN for recognizing G or A;
- NS for recognizing A or C or G or T;
- HG for recognizing T;
- IG for recognizing T;
- NK for recognizing G;
- HA for recognizing C;
- ND for recognizing C;
- HI for recognizing C;
- HN for recognizing G;
- NA for recognizing G;
- SN for recognizing G or A; and
- YG for recognizing T;

(b) binding the same nucleic acid target sequence with another transcription activator-like effector (TALE) protein comprising a plurality of TALE-like repeat sequences, similar to that used in step a), wherein at least one RVD has been replaced by a RVD consisting of X* or **, preferably H*, T*, Q* or N*, wherein

- X represents one amino acid residue selected from the group of A,G, V, L, I, M, S, T, C, P, D, E, F, Y, W, Q, N, H, R and K,
- and * represents a gap in one position of the RVD,

(c) determining the binding affinity with said nucleic acid sequence under a) and b),

(d) calculating the ratio of binding activities determined under c) , wherein said ratio, when close to 0, indicates the presence of chemically modified nucleic acid in said nucleic acid target sequence and, when close to 1, the absence of chemically modified nucleic acid in said nucleic acid target sequence.

18. The method according to claim 17 wherein binding affinity is measured by a nuclease activity.

19. The method according to claim 17 wherein binding affinity is measured by a transcriptional activity.

20. The method according to claim 17 wherein binding affinity is measured by detecting signal of fluorescent proteins fused to said TALE proteins of (a) and (b).

CLAIMS

1. An invention not claimed in any divisional application.