

CLAIMS

What is claimed is:

1. An engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) - Cas system of CLUST.091979 comprising:
 - (a) a CRISPR-associated protein or a nucleic acid encoding the CRISPR-associated protein, wherein the CRISPR-associated protein comprises an amino acid sequence of SEQ ID NO: 241; and
 - (b) an RNA guide comprising a direct repeat sequence and a spacer sequence capable of hybridizing to a target nucleic acid;wherein the CRISPR-associated protein is capable of binding to the RNA guide and of modifying the target nucleic acid sequence complementary to the spacer sequence.
2. The system of claim 1, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 80% (*e.g.*, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in SEQ ID NO: 4, SEQ ID NO: 10, SEQ ID NO: 12, or SEQ ID NO: 14.
3. An engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) - Cas system of CLUST.091979 comprising:
 - (a) a CRISPR-associated protein or a nucleic acid encoding the CRISPR-associated protein, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 80% (*e.g.*, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in any one of SEQ ID NOs: 1-56; and
 - (b) an RNA guide comprising a direct repeat sequence and a spacer sequence capable of hybridizing to a target nucleic acid;wherein the CRISPR-associated protein is capable of binding to the RNA guide and of modifying the target nucleic acid sequence complementary to the spacer sequence.
4. The system of any previous claim, wherein the CRISPR-associated protein comprises at least one RuvC domain or at least one split RuvC domain.

5. ~~The system of any previous claim, wherein the CRISPR-associated protein comprises one or more of the following sequences:~~
- (a) ~~PX₁X₂X₃X₄F (SEQ ID NO: 216), wherein X₁ is L or M or I or C or F, X₂ is Y or W or F, X₃ is K or T or C or R or W or Y or H or V, and X₄ is I or L or M;~~
 - (b) ~~RX₁X₂X₃L (SEQ ID NO: 217), wherein X₁ is I or L or M or Y or T or F, X₂ is R or Q or K or E or S or T, and X₃ is L or I or T or C or M or K;~~
 - (c) ~~NX₁YX₂ (SEQ ID NO: 218), wherein X₁ is I or L or F and X₂ is K or R or V or E;~~
 - (d) ~~KX₁X₂X₃FAX₄X₅KD (SEQ ID NO: 219), wherein X₁ is T or I or N or A or S or F or V, X₂ is I or V or L or S, X₃ is H or S or G or R, X₄ is D or S or E, and X₅ is I or V or M or T or N;~~
 - (e) ~~LX₁NX₂ (SEQ ID NO: 220), wherein X₁ is G or S or C or T and X₂ is N or Y or K or S;~~
 - (f) ~~PX₁X₂X₃X₄SQX₅DS (SEQ ID NO: 221), wherein X₁ is S or P or A, X₂ is Y or S or A or P or E or Y or Q or N, X₃ is F or Y or H, X₄ is T or S, and X₅ is M or T or I;~~
 - (g) ~~KX₁X₂VRX₃X₄QEX₅H (SEQ ID NO: 222), wherein X₁ is N or K or W or R or E or T or Y, X₂ is M or R or L or S or K or V or E or T or I or D, X₃ is L or R or H or P or T or K or Q or P or S or A, X₄ is G or Q or N or R or K or E or I or T or S or C, and X₅ is R or W or Y or K or T or F or S or Q; and~~
 - (h) ~~X₁NGX₂X₃X₄DX₅NX₆X₇X₈N (SEQ ID NO: 223), wherein X₁ is I or K or V or L, X₂ is L or M, X₃ is N or H or P, X₄ is A or S or C, X₅ is V or Y or I or F or T or N, X₆ is A or S, X₇ is S or A or P, and X₈ is M or C or L or R or N or S or K or L.~~
6. ~~The system of any previous claim, wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in any one of SEQ ID NOs: 57-90, SEQ ID NOs: 118-151, or SEQ ID NO: 213.~~
7. ~~The system of any previous claim, wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in any one of SEQ ID NOs: 57-90, SEQ ID NOs: 118-151, or SEQ ID NO: 213.~~
8. ~~The system of any previous claim, wherein the direct repeat sequence comprises one or more of the following sequences:~~

- (a) ~~X₁X₂TX₃X₄X₅X₆X₇X₈ (SEQ ID NO: 224), wherein X₁ is A or C or G, X₂ is T or C or A, X₃ is T or G or A, X₄ is T or G, X₅ is T or G or A, X₆ is G or T or A, X₇ is T or G or A, and X₈ is A or G or T;~~
- (b) ~~X₁X₂X₃X₄X₅X₆X₇X₈X₉ (SEQ ID NO: 226), wherein X₁ is T or C or A, X₂ is T or A or G, X₃ is T or C or A, X₄ is T or A, X₅ is T or A or G, X₆ is T or A, X₇ is A or T, X₈ is A or G or C or T, and X₉ is G or A or C; and~~
- (c) ~~X₁X₂X₃AC (SEQ ID NO: 228), wherein X₁ is A or C or G, X₂ is C or A, and X₃ is A or C.~~
9. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 57.~~
10. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 57.~~
11. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the CRISPR-associated protein is capable of recognizing a protospacer adjacent motif (PAM) sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' TNNT 3' or 5' TNRT 3', wherein "N" is any nucleotide and "R" is A or G.~~
12. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' TNNT 3' or 5' TNRT 3', wherein "N" is any nucleotide and "R" is A or G.~~

13. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~
14. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~
15. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3', 5' NTTR 3' (e.g., 5' TTTG 3'), or 5' NNR 3', wherein "N" is any nucleotide and "R" is A or G.~~
16. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3', 5' NTTR 3' (e.g., 5' TTTG 3'), or 5' NNR 3', wherein "N" is any nucleotide and "R" is A or G.~~
17. ~~The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~

- ~~18. The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~
- ~~19. The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3' or 5' RTTR 3' (e.g., 5' ATTG 3' or 5' GTTA 3'), wherein "N" is any nucleotide and "R" is A or G.~~
- ~~20. The system of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth 5' NTTN 3' or 5' RTTR 3' (e.g., 5' ATTG 3' or 5' GTTA 3'), wherein "N" is any nucleotide and "R" is A or G.~~
- ~~215.~~ The system of any previous claim, wherein the spacer sequence of the RNA guide comprises between about 15 nucleotides to about 55 nucleotides.
- ~~226.~~ The system of any previous claim, wherein the spacer sequence of the RNA guide comprises between 20 and 45 nucleotides.
- ~~23. The system of any previous claim, wherein the CRISPR-associated protein comprises a catalytic residue (e.g., aspartic acid or glutamic acid).~~
- ~~24. The system of any previous claim, wherein the CRISPR-associated protein cleaves the target nucleic acid.~~
- ~~257.~~ The system of any previous claim, wherein the CRISPR-associated protein further comprises a peptide tag, a fluorescent protein, a base-editing domain, a DNA methylation domain, a histone

residue modification domain, a localization factor, a transcription modification factor, a light-gated control factor, a chemically inducible factor, or a chromatin visualization factor.

268. The system of any previous claim, wherein the nucleic acid encoding the CRISPR-associated protein is codon-optimized for expression in a cell.

279. The system of any previous claim, wherein the nucleic acid encoding the CRISPR-associated protein is operably linked to a promoter.

2810. The system of any previous claim, wherein the nucleic acid encoding the CRISPR-associated protein is in a vector.

2911. The system of claim 28, wherein the vector comprises a retroviral vector, a lentiviral vector, a phage vector, an adenoviral vector, an adeno-associated vector, or a herpes simplex vector.

~~30. The system of any previous claim, wherein the target nucleic acid is a DNA molecule.~~

~~31. The system of any previous claim, wherein the CRISPR-associated protein comprises non-specific nuclease activity.~~

~~32. The system of any previous claim, wherein recognition of the target nucleic acid by the CRISPR-associated protein and RNA guide results in a modification of the target nucleic acid.~~

~~33. The system of claim 32, wherein the modification of the target nucleic acid is a double-stranded cleavage event.~~

~~34. The system of claim 32, wherein the modification of the target nucleic acid is a single-stranded cleavage event.~~

~~35. The system of any previous claim, wherein the modification of the target nucleic acid results in an insertion event.~~

~~36. The system of any previous claim, wherein the modification of the target nucleic acid results in a deletion event.~~

~~37. The system of any previous claim, wherein the modification of the target nucleic acid results in cell toxicity or cell death.~~

~~38. The system of any previous claim, further comprising a donor template nucleic acid.~~

~~39. The system of claim 38, wherein the donor template nucleic acid is a DNA molecule.~~

~~40. The system of claim 38, wherein the donor template nucleic acid is an RNA molecule.~~

~~41. The system of any previous claim, wherein the RNA guide optionally comprises a tracrRNA.~~

~~42~~12. The system of any previous claim, wherein the system does not comprise a tracrRNA.

~~43. The system of any previous claim, wherein the CRISPR-associated protein is self-processing.~~

~~44~~13. The system of any previous claim, wherein the system is present in a delivery composition comprising a nanoparticle, a liposome, an exosome, a microvesicle, or a gene-gun.

~~45~~14. The system of any previous claim, within a cell.

~~46. The system of claim 45, wherein the cell is a eukaryotic cell.~~

~~47. The system of claim 45, wherein the cell is a prokaryotic cell.~~

~~48~~15. A cell, wherein the cell comprises:

- (a) a CRISPR-associated protein or a nucleic acid encoding the CRISPR-associated protein, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in any one of SEQ ID NOs: 1-56; and
- (b) an RNA guide comprising a direct repeat sequence and a spacer sequence capable of hybridizing to a target nucleic acid.

~~49~~16. The cell of claim ~~48~~15, wherein the CRISPR-associated protein comprises one or more of the following sequences:

- (a) $PX_1X_2X_3X_4F$ (SEQ ID NO: 216), wherein X_1 is L or M or I or C or F, X_2 is Y or W or F, X_3 is K or T or C or R or W or Y or H or V, and X_4 is I or L or M;
- (b) $RX_1X_2X_3L$ (SEQ ID NO: 217), wherein X_1 is I or L or M or Y or T or F, X_2 is R or Q or K or E or S or T, and X_3 is L or I or T or C or M or K;
- (c) NX_1YX_2 (SEQ ID NO: 218), wherein X_1 is I or L or F and X_2 is K or R or V or E;
- (d) $KX_1X_2X_3FAX_4X_5KD$ (SEQ ID NO: 219), wherein X_1 is T or I or N or A or S or F or V, X_2 is I or V or L or S, X_3 is H or S or G or R, X_4 is D or S or E, and X_5 is I or V or M or T or N;
- (e) LX_1NX_2 (SEQ ID NO: 220), wherein X_1 is G or S or C or T and X_2 is N or Y or K or S;
- (f) $PX_1X_2X_3X_4SQX_5DS$ (SEQ ID NO: 221), wherein X_1 is S or P or A, X_2 is Y or S or A or P or E or Y or Q or N, X_3 is F or Y or H, X_4 is T or S, and X_5 is M or T or I;
- (g) $KX_1X_2VRX_3X_4QEX_5H$ (SEQ ID NO: 222), wherein X_1 is N or K or W or R or E or T or Y, X_2 is M or R or L or S or K or V or E or T or I or D, X_3 is L or R or H or P or T or K or Q or P or S or A, X_4 is G or Q or N or R or K or E or I or T or S or C, and X_5 is R or W or Y or K or T or F or S or Q; and
- (h) $X_1NGX_2X_3X_4DX_5NX_6X_7X_8N$ (SEQ ID NO: 223), wherein X_1 is I or K or V or L, X_2 is L or M, X_3 is N or H or P, X_4 is A or S or C, X_5 is V or Y or I or F or T or N, X_6 is A or S, X_7 is S or A or P, and X_8 is M or C or L or R or N or S or K or L.

~~50. The cell of any previous claim, wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in any one of SEQ ID NOs: 57-90, SEQ ID NOs: 118-151, or SEQ ID NO: 213.~~

~~51. The cell of any previous claim, wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in any one of SEQ ID NOs: 57-90, SEQ ID NOs: 118-151, or SEQ ID NO: 213.~~

~~52. The cell of any previous claim, wherein the direct repeat sequence comprises one or more of the following sequences:~~

- (a) ~~X₁X₂TX₃X₄X₅X₆X₇X₈ (SEQ ID NO: 224), wherein X₁ is A or C or G, X₂ is T or C or A, X₃ is T or G or A, X₄ is T or G, X₅ is T or G or A, X₆ is G or T or A, X₇ is T or G or A, and X₈ is A or G or T;~~
- (b) ~~X₁X₂X₃X₄X₅X₆X₇X₈X₉ (SEQ ID NO: 226), wherein X₁ is T or C or A, X₂ is T or A or G, X₃ is T or C or A, X₄ is T or A, X₅ is T or A or G, X₆ is T or A, X₇ is A or T, X₈ is A or G or C or T, and X₉ is G or A or C; and~~
- (c) ~~X₁X₂X₃AC (SEQ ID NO: 228), wherein X₁ is A or C or G, X₂ is C or A, and X₃ is A or C.~~
53. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 57.~~
54. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 57.~~
55. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' TNNT 3' or 5' TNRT 3', wherein "N" is any nucleotide and "R" is A or G.~~
56. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' TNNT 3' or 5' TNRT 3', wherein "N" is any nucleotide and "R" is A or G.~~

57. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~
58. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~
59. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3', 5' NTTR 3' (e.g., 5' TTTG 3'), or 5' NNR 3', wherein "N" is any nucleotide and "R" is A or G.~~
60. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3', 5' NTTR 3' (e.g., 5' TTTG 3'), or 5' NNR 3', wherein "N" is any nucleotide and "R" is A or G.~~
61. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~

62. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~
63. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3' or 5' RTTR 3' (e.g., 5' ATTG 3' or 5' GTTA 3'), wherein "N" is any nucleotide and "R" is A or G.~~
64. ~~The cell of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth 5' NTTN 3' or 5' RTTR 3' (e.g., 5' ATTG 3' or 5' GTTA 3'), wherein "N" is any nucleotide and "R" is A or G.~~
65. ~~The cell of any previous claim, wherein the spacer sequence comprises between about 15 nucleotides to about 55 nucleotides.~~
66. ~~The cell of any previous claim, wherein the spacer sequence comprises between 20 and 45 nucleotides.~~
67. ~~The cell of any previous claim, wherein the cell further comprises a tracrRNA.~~
68. ~~The cell of any previous claim, wherein the system does not comprise a tracrRNA.~~
69. ~~The cell of any previous claim, wherein the cell is a eukaryotic cell, e.g., a mammalian cell, e.g., a human cell.~~
70. ~~The cell of any previous claim, wherein the cell is a prokaryotic cell.~~

~~71~~17. An *in vitro* method of binding the system of any previous claim to a target nucleic acid in a cell comprising:

- (a) providing the system; and
- (b) delivering the system to the cell,

wherein the cell comprises the target nucleic acid, wherein the CRISPR-associated-protein binds to the RNA guide, and wherein the spacer sequence binds to the target nucleic acid.

~~72. The method of claim 71, wherein the cell is a eukaryotic cell, e.g., a mammalian cell, e.g., a human cell.~~

7318. An *in vitro* method of modifying a target nucleic acid, the method comprising delivering to the target nucleic acid an engineered, non-naturally occurring CRISPR-Cas system comprising:

- (a) a CRISPR-associated protein or a nucleic acid encoding the CRISPR-associated protein, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in any one of SEQ ID NOs: 1-56; and
- (b) an RNA guide comprising a direct repeat sequence and a spacer sequence capable of hybridizing to the target nucleic acid;

wherein the CRISPR-associated protein is capable of binding to the RNA guide; and

wherein recognition of the target nucleic acid by the CRISPR-associated protein and RNA guide results in a modification of the target nucleic acid.

7419. The method of claim 7318, wherein the CRISPR-associated protein comprises one or more of the following sequences:

- (a) $PX_1X_2X_3X_4F$ (SEQ ID NO: 216), wherein X_1 is L or M or I or C or F, X_2 is Y or W or F, X_3 is K or T or C or R or W or Y or H or V, and X_4 is I or L or M;
- (b) $RX_1X_2X_3L$ (SEQ ID NO: 217), wherein X_1 is I or L or M or Y or T or F, X_2 is R or Q or K or E or S or T, and X_3 is L or I or T or C or M or K;
- (c) NX_1YX_2 (SEQ ID NO: 218), wherein X_1 is I or L or F and X_2 is K or R or V or E;
- (d) $KX_1X_2X_3FAX_4X_5KD$ (SEQ ID NO: 219), wherein X_1 is T or I or N or A or S or F or V, X_2 is I or V or L or S, X_3 is H or S or G or R, X_4 is D or S or E, and X_5 is I or V or M or T or N;
- (e) LX_1NX_2 (SEQ ID NO: 220), wherein X_1 is G or S or C or T and X_2 is N or Y or K or S;

- (f) $PX_1X_2X_3X_4SQX_5DS$ (SEQ ID NO: 221), wherein X_1 is S or P or A, X_2 is Y or S or A or P or E or Y or Q or N, X_3 is F or Y or H, X_4 is T or S, and X_5 is M or T or I;
- (g) $KX_1X_2VRX_3X_4QEX_5H$ (SEQ ID NO: 222), wherein X_1 is N or K or W or R or E or T or Y, X_2 is M or R or L or S or K or V or E or T or I or D, X_3 is L or R or H or P or T or K or Q or P or S or A, X_4 is G or Q or N or R or K or E or I or T or S or C, and X_5 is R or W or Y or K or T or F or S or Q; and
- (h) $X_1NGX_2X_3X_4DX_5NX_6X_7X_8N$ (SEQ ID NO: 223), wherein X_1 is I or K or V or L, X_2 is L or M, X_3 is N or H or P, X_4 is A or S or C, X_5 is V or Y or I or F or T or N, X_6 is A or S, X_7 is S or A or P, and X_8 is M or C or L or R or N or S or K or L.

~~75. The method of any previous claim, wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in any one of SEQ ID NOs: 57-90, SEQ ID NOs: 118-151, or SEQ ID NO: 213.~~

~~76. The method of any previous claim, wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in any one of SEQ ID NOs: 57-90, SEQ ID NOs: 118-151, or SEQ ID NO: 213.~~

~~77. The method of any previous claim, wherein the direct repeat sequence comprises one or more of the following sequences:~~

- ~~(a) $X_1X_2TX_3X_4X_5X_6X_7X_8$ (SEQ ID NO: 224), wherein X_1 is A or C or G, X_2 is T or C or A, X_3 is T or G or A, X_4 is T or G, X_5 is T or G or A, X_6 is G or T or A, X_7 is T or G or A, and X_8 is A or G or T;~~
- ~~(b) $X_1X_2X_3X_4X_5X_6X_7X_8X_9$ (SEQ ID NO: 226), wherein X_1 is T or C or A, X_2 is T or A or G, X_3 is T or C or A, X_4 is T or A, X_5 is T or A or G, X_6 is T or A, X_7 is A or T, X_8 is A or G or C or T, and X_9 is G or A or C; and~~
- ~~(c) $X_1X_2X_3AC$ (SEQ ID NO: 228), wherein X_1 is A or C or G, X_2 is C or A, and X_3 is A or C.~~

~~78. The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g.,~~

~~81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 57.~~

~~79. The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 57.~~

~~80. The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' TNNT 3' or 5' TNRT 3', wherein "N" is any nucleotide and "R" is A or G.~~

~~81. The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 1, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' TNNT 3' or 5' TNRT 3', wherein "N" is any nucleotide and "R" is A or G.~~

~~82. The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~

~~83. The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~

84. ~~The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3', 5' NTTR 3' (e.g., 5' TTTG 3'), or 5' NNR 3', wherein "N" is any nucleotide and "R" is A or G.~~
85. ~~The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 4, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3', 5' NTTR 3' (e.g., 5' TTTG 3'), or 5' NNR 3', wherein "N" is any nucleotide and "R" is A or G.~~
86. ~~The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~
87. ~~The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the direct repeat sequence comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~
88. ~~The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3' or 5' RTTR 3' (e.g., 5' ATTG 3' or 5' GTTA 3'), wherein "N" is any nucleotide and "R" is A or G.~~

89. ~~The method of any previous claim, wherein the CRISPR-associated protein is a protein having at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identity to an amino acid sequence set forth in SEQ ID NO: 10, and wherein the CRISPR-associated protein is capable of recognizing a PAM sequence, wherein the PAM sequence comprises a nucleic acid sequence set forth 5' NTTN 3' or 5' RTTR 3' (e.g., 5' ATTG 3' or 5' GTTA 3'), wherein "N" is any nucleotide and "R" is A or G.~~
90. ~~The method of any previous claim, wherein the spacer sequence comprises between about 15 nucleotides to about 55 nucleotides.~~
91. ~~The method of any previous claim, wherein the spacer sequence comprises between 20 and 45 nucleotides.~~
92. ~~The method of any previous claim, wherein the system further comprises a tracrRNA.~~
93. ~~The method of any previous claim, wherein the system does not comprise a tracrRNA.~~
94. ~~The method of any previous claim, wherein the target nucleic acid is a DNA molecule.~~
95. ~~The method of any previous claim, wherein the CRISPR-associated protein comprises non-specific nuclease activity.~~
96. ~~The method of any previous claim, wherein the modification of the target nucleic acid is a double-stranded cleavage event.~~
97. ~~The method of any previous claim, wherein the modification of the target nucleic acid is a single-stranded cleavage event.~~
98. ~~The method of any previous claim, wherein the modification of the target nucleic acid results in an insertion event.~~
99. ~~The method of any previous claim, wherein the modification of the target nucleic acid results in a deletion event.~~

- ~~100. —The method of any previous claim, wherein the modification of the target nucleic acid results in cell toxicity or cell death.~~
- ~~101. —A method of editing a target nucleic acid, the method comprising contacting the target nucleic acid with the system of any previous claim.~~
- ~~102. A method of modifying expression of a target nucleic acid, the method comprising contacting the target nucleic acid with a system of any previous claim.~~
- ~~103. —A method of targeting the insertion of a payload nucleic acid at a site of a target nucleic acid, the method comprising contacting the target nucleic acid with a system of any previous claim.~~
- ~~104. —A method of targeting the excision of a payload nucleic acid from a site at a target nucleic acid, the method comprising contacting the target nucleic acid with a system of any previous claim.~~
- ~~105. —A method of non-specifically degrading single stranded DNA upon recognition of a DNA target nucleic acid, the method comprising contacting the target nucleic acid with a system of any previous claim.~~
- ~~106. —A method of detecting a target nucleic acid in a sample, the method comprising:~~
- ~~(a) —contacting the sample with the system of any previous claim and a labeled reporter nucleic acid, wherein hybridization of the spacer sequence to the target nucleic acid causes cleavage of the labeled reporter nucleic acid; and~~
 - ~~(b) —measuring a detectable signal produced by cleavage of the labeled reporter nucleic acid, thereby detecting the presence of the target nucleic acid in the sample.~~
- ~~107. —Use of the system of any previous claim in an *in vitro* or *ex vivo* method of:~~
- ~~(a) —targeting and editing a target nucleic acid;~~
 - ~~(b) —non-specifically degrading a single stranded nucleic acid upon recognition of the nucleic acid;~~
 - ~~(c) —targeting and nicking a non-spacer complementary strand of a double stranded target upon recognition of a spacer complementary strand of the double stranded target;~~
 - ~~(d) —targeting and cleaving a double stranded target nucleic acid;~~
 - ~~(e) —detecting a target nucleic acid in a sample;~~

- ~~(f) — specifically editing a double-stranded nucleic acid;~~
- ~~(g) — base editing a double-stranded nucleic acid;~~
- ~~(h) — inducing genotype-specific or transcriptional state-specific cell death or dormancy in a cell;~~
- ~~(i) — creating an indel in a double-stranded nucleic acid target;~~
- ~~(j) — inserting a sequence into a double-stranded nucleic acid target; or~~
- ~~(k) — deleting or inverting a sequence in a double-stranded nucleic acid target.~~

~~108. — A method of introducing an insertion or deletion into a target nucleic acid in a mammalian cell, comprising a transfection of:~~

- ~~(a) — a nucleic acid sequence encoding a CRISPR-associated protein, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in any one of SEQ ID NOs: 1-56; and~~
 - ~~(b) — an RNA guide (or a nucleic acid encoding the RNA guide) comprising a direct repeat sequence and a spacer sequence capable of hybridizing to the target nucleic acid;~~
- ~~wherein the CRISPR-associated protein is capable of binding to the RNA guide; and~~
- ~~wherein recognition of the target nucleic acid by the CRISPR-associated protein and RNA guide results in a modification of the target nucleic acid.~~

~~109. — The method of claim 108, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in SEQ ID NO: 4.~~

~~110. — The method of any previous claim, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in SEQ ID NO: 4.~~

~~111. — The method of any previous claim, wherein the direct repeat comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~

- ~~112. The method of any previous claim, wherein the direct repeat comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 60.~~
- ~~113. The method of any previous claim, wherein the target nucleic acid is adjacent to a PAM sequence, and the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3', 5' NTTR 3' (e.g., 5' TTTG 3'), or 5' NNR 3', wherein "N" is any nucleotide and "R" is A or G.~~
- ~~114. The method of claim 108, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in SEQ ID NO: 10.~~
- ~~115. The method of any previous claim, wherein the CRISPR-associated protein comprises an amino acid sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to an amino acid sequence set forth in SEQ ID NO: 10.~~
- ~~116. The method of any previous claim, wherein the direct repeat comprises a nucleotide sequence that is at least 80% (e.g., 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~
- ~~117. The method of any previous claim, wherein the direct repeat comprises a nucleotide sequence that is at least 95% (e.g., 95%, 96%, 97%, 98%, 99% or 100%) identical to a nucleotide sequence set forth in SEQ ID NO: 62 or SEQ ID NO: 213.~~
- ~~118. The method of any previous claim, wherein the target nucleic acid is adjacent to a PAM sequence, and the PAM sequence comprises a nucleic acid sequence set forth as 5' NTTN 3' or 5' RTTR 3' (e.g., 5' ATTG 3' or 5' GTTA 3'), wherein "N" is any nucleotide and "R" is A or G.~~
- ~~119. The method of any previous claim, wherein the transfection is a transient transfection.~~
- ~~120. The method of any previous claim wherein the cell is a human cell.~~

~~121~~20. A composition comprising:

- (a) a CRISPR-associated protein or a nucleic acid encoding the CRISPR-associated protein, and
- (b) an RNA guide comprising a direct repeat sequence and a spacer sequence;

wherein the CRISPR-associated protein comprises one or more of the following amino acid sequences:

- (i) $PX_1X_2X_3X_4F$ (SEQ ID NO: 216), wherein X_1 is L or M or I or C or F, X_2 is Y or W or F, X_3 is K or T or C or R or W or Y or H or V, and X_4 is I or L or M;
- (ii) $RX_1X_2X_3L$ (SEQ ID NO: 217), wherein X_1 is I or L or M or Y or T or F, X_2 is R or Q or K or E or S or T, and X_3 is L or I or T or C or M or K;
- (iii) NX_1YX_2 (SEQ ID NO: 218), wherein X_1 is I or L or F and X_2 is K or R or V or E;
- (iv) $KX_1X_2X_3FAX_4X_5KD$ (SEQ ID NO: 219), wherein X_1 is T or I or N or A or S or F or V, X_2 is I or V or L or S, X_3 is H or S or G or R, X_4 is D or S or E, and X_5 is I or V or M or T or N;
- (v) LX_1NX_2 (SEQ ID NO: 220), wherein X_1 is G or S or C or T and X_2 is N or Y or K or S;
- (vi) $PX_1X_2X_3X_4SQX_5DS$ (SEQ ID NO: 221), wherein X_1 is S or P or A, X_2 is Y or S or A or P or E or Y or Q or N, X_3 is F or Y or H, X_4 is T or S, and X_5 is M or T or I;
- (vii) $KX_1X_2VRX_3X_4QEX_5H$ (SEQ ID NO: 222), wherein X_1 is N or K or W or R or E or T or Y, X_2 is M or R or L or S or K or V or E or T or I or D, X_3 is L or R or H or P or T or K or Q or P or S or A, X_4 is G or Q or N or R or K or E or I or T or S or C, and X_5 is R or W or Y or K or T or F or S or Q; and
- (viii) $X_1NGX_2X_3X_4DX_5NX_6X_7X_8N$ (SEQ ID NO: 223), wherein X_1 is I or K or V or L, X_2 is L or M, X_3 is N or H or P, X_4 is A or S or C, X_5 is V or Y or I or F or T or N, X_6 is A or S, X_7 is S or A or P, and X_8 is M or C or L or R or N or S or K or L; and

wherein the CRISPR-associated protein binds to the RNA guide, and the spacer binds to a target nucleic acid.

21. The system of any one of claims 1-14, the cell of any one of claims 15-16 or the composition of claim 20 for use in medicine.