

CLAIMS

1. A system comprising:
 - (i) a sequence-targeting component or a polynucleotide encoding the same, said component comprising a target fusion protein having
 - (a) a sequence-targeting protein which is a nickase Cas9 protein, and
 - (b) a first uracil DNA glycosylase (UNG) inhibitor peptide (UGI);
 - (ii) an RNA scaffold, or a DNA polynucleotide encoding the same, said scaffold comprising
 - (a) a nucleic acid-targeting motif comprising a guide RNA sequence that is complementary to a target nucleic acid sequence,
 - (b) an RNA motif capable of binding to the sequence-targeting protein, and
 - (c) a first recruiting RNA motif, and
 - (iii) a first effector fusion protein, or a polynucleotide encoding the same, said protein comprising
 - (a) a first RNA binding domain capable of binding to the first recruiting RNA motif,
 - (b) a linker, and
 - (c) an effector domain,wherein the first effector fusion protein or the effector domain has a cytidine deamination activity or adenosine deamination activity.
2. The system of claim 1, wherein the target fusion protein further comprises two or more UGIs.
3. The system of claim 1, wherein the RNA scaffold further comprises two or more recruiting RNA motifs.
4. The system of any one of claims 1-3, wherein one or more of the polynucleotides encoding the sequence-targeting protein, the first UGI, the second UGI, the RNA binding domain, and the effector domain are optimized for eukaryotic or mammalian cell expression.
5. The system of claims 1-4, wherein the sequence-targeting component or the first effector fusion protein comprises one or more nuclear localization signals (NLSs).

6. The system of claim 5, wherein the sequence-targeting component comprises two NLSs.
7. The system of any one of claims 1-6, wherein the sequence-targeting protein comprises the sequence of nCas9 of a species selected from the group consisting of *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Staphylococcus aureus*, *Streptococcus thermophilus*, *Neisseria meningitidis*, and *Treponema denticola*.
8. The system of any one of claims 1-7, wherein the first recruiting RNA motif and the first RNA binding domain are a pair selected from the group consisting of:
- a telomerase Ku binding motif and Ku protein or an RNA-binding section thereof,
 - a telomerase Sm7 binding motif and Sm7 protein or an RNA-binding section thereof,
 - a MS2 phage operator stem-loop and MS2 coat protein (MCP) or an RNA-binding section thereof,
 - a PP7 phage operator stem-loop and PP7 coat protein (PCP) or an RNA-binding section thereof,
 - a SfMu phage Com stem-loop and Com RNA binding protein or an RNA-binding section thereof,
 - a chemically modified version of the above recruiting RNA motifs and their corresponding RNA binding domains, and
 - a non-natural RNA aptamer and corresponding aptamer ligand or an RNA-binding section thereof.
9. The system of any one of claims 1-8, wherein the effector of cytidine deamination activity is a wild type or genetically engineered version of AID, CDA, APOBEC1, APOBEC3A, APOBEC3B, APOBEC3C, APOBEC3D, APOBEC3F, or other APOBEC family enzymes of a species selected from the group consisting of human, rat, mouse, bat, naked mole rat, elephant, chicken, lizard, giant tortoise, coelacanth, and other vertebrate species.
10. The system of any one of claims 1-9, wherein the effector of adenosine deamination activity is a wild type or genetically engineered version of ADA, ADAR family enzymes, or tRNA

adenosine deaminases of a species selected from the group consisting of bacteria, yeast, human, rat, mouse, bat, naked mole rat, elephant, chicken, lizard, giant tortoise, coelacanth, and other vertebrate species.

11. An isolated nucleic acid encoding components (i)-(iii) of the system of any one of claims 1-10.

12. An expression vector or a host cell comprising the nucleic acid of claim 11.

13. An *in vitro* or *ex vivo* method of site-specific modification of a target nucleic acid, comprising contacting the target nucleic acid with the system of any one of claims 1-10.

14. The method of claim 13, wherein the target nucleic acid is in a cell.

15. The method of claim 14, wherein the target nucleic acid is extrachromosomal DNA.

16. The method of claim 14, wherein the target nucleic acid is a genomic DNA on a chromosome.

17. The method of any one of claims 14-16, wherein the cell is selected from the group consisting of an archaeal cell, a bacterial cell, a eukaryotic cell, a eukaryotic single-cell organism, a somatic cell, a germ cell, a stem cell, a plant cell, an algal cell, an animal cell, in invertebrate cell, a vertebrate cell, a fish cell, a frog cell, a bird cell, a mammalian cell, a pig cell, a cow cell, a goat cell, a sheep cell, a rodent cell, a rat cell, a mouse cell, a horse cell, a non-human primate cell, and a human cell.

18. The method of claim 17, wherein the cell is a plant cell.

19. The method of claim 17, wherein the cell is derived from a human or non-human subject.

20. The method of claim 19, wherein the human or non-human subject has a genetic mutation of a gene.
21. The method of claim 20, wherein the subject has a disorder caused by the genetic mutation or is at risk of having the disorder.
22. The method of any one of claims 19-21, wherein said site-specific modification corrects a genetic mutation or inactivates the expression of a gene or changes the expression levels of a gene or changes intron-exon splicing.
23. The method of claim 19, wherein the subject has a pathogen or is at risk of being exposed to the pathogen.
24. The method of claim 23, wherein said site-specific modification inactivates a gene of the pathogen.
25. A kit comprising the system of any one of claims 1-10.
26. The kit of claim 25 further comprising one or more components selected from the group consisting of a reagent for reconstitution and/or dilution and a reagent for introducing nucleic acid or polypeptide into a host cell.