CLAIMS

1. A composition comprising a CRISPR-Cas system, comprising:

(a) a Type-V Cas protein comprising a RuvC nuclease domain but not comprising a HNH domain, or a polynucleotide encoding the Type-V Cas protein, and

(b) a Type-V CRISPR-Cas system guide engineered to hybridize with a target sequence adjacent to a protospacer motif (PAM) in the genome of a eukaryotic cell, or a polynucleotide encoding the Type-V CRISPR-Cas system guide, in which the engineered Type-V CRISPR-Cas system guide is capable of forming a CRISPR complex with the Type-V Cas protein.

2. A composition according to Claim 1, in which the composition comprises the Type-V CRISPR-Cas system guide and the Type-V Cas protein.

3. A composition according to Claim 1, in which the composition comprises a CRISPR complex formed by the Type-V CRISPR-Cas system guide and the Type-V Cas protein.

4. A composition according to Claim 1, in which the composition comprises one or more vectors encoding the Type-V CRISPR-Cas system guide and the Type-V Cas protein.

5. A composition according to Claim 4, in which the composition comprises one or more viral vectors encoding the Type-V CRISPR-Cas system guide and the Type-V Cas protein.

6. A composition according to Claim 5, in which the viral vectors comprise an adenoviral vector, a lentiviral vector, or an adeno-associated viral vector.

7. A composition according to Claim 1, in which the composition comprises an mRNA encoding the Type-V Cas protein.

8. A composition according to Claim 7, in which the mRNA encoding the Type-V Cas protein is comprised in a lipid nanoparticle, a liposome, an exosome, or a microvesicle.

9. A composition according to Claim 1, in which the Type-V Cas protein is linked to at least one nuclear localization signal.

10. A composition according to Claim 1, in which the Type-V Cas protein is from *Francisella tularensis* 1, *Prevotella albensis*, *Lachnospiraceae* bacterium MC2017 1, *Butyrivibrio proteoclasticus*, *Peregrinibacteria* bacterium GW2011_GWA2_33_10,

Parcubacteria bacterium GW2011_GWC2_44_17, *Smithella* sp. SCADC, *Acidaminococcus* sp. BV3L6, *Lachnospiraceae* bacterium MA2020, *Candidatus* Methanoplasma termitum, *Eubacterium eligens*, *Moraxella bovoculi* 237, *Leptospira inadai*, *Lachnospiraceae* bacterium ND2006, *Porphyromonas crevioricanis* 3, *Prevotella disiens*, or *Porphyromonas macacae*.

11. A composition according to Claim 1, in which the Type-V Cas protein is *Francisella novicida* U112 Cpf1 (FnCpf1), *Acidaminococcus* sp. BV3L6 Cpf1 (AsCpf1), or *Lachnospiraceae* bacterium ND2006 (LbCpf1).

12. A composition according to Claim 1, in which the Type-V Cas protein comprises at least one mutation in a catalytic domain.

13. A composition according to Claim 1, in which the Type-V Cas protein comprises at least one mutation in a catalytic domain and is linked to a heterologous functional domain.

14. A composition according to Claim 13, in which the heterologous functional domain has one or more of the following activities: methylase activity, demethylase activity, transcription activation activity, transcription repression activity, transcription release factor activity, histone modification activity, nuclease activity, single-strand RNA cleavage activity, double-strand RNA cleavage activity, single-strand DNA cleavage activity, double-strand DNA cleavage activity, and nucleic acid binding activity.

15. A composition according to Claim 1, in which the composition comprises or encodes multiple Type-V CRISPR-Cas system guides each engineered to hybridize with a different target sequence.

16. A composition according to Claim 1, in which the Type-V CRISPR-Cas system guide comprises a guide sequence linked to a direct repeat sequence, in which the direct repeat sequence is encoded by any of SEQ ID NOs:195-210 or comprises any of SEQ ID NOs:1434-1449.

17. A composition according to Claim 1, in which the Type-V CRISPR-Cas system guide comprises one or more modified nucleotides or one or more non-nucleotide moieties.

18. A composition according to Claim 1, in which the Type-V CRISPR-Cas system guide comprises at least one chemical modification, in which the chemical modification is a methylene bridge between carbon atoms of a ribose ring, a phosphorothioate linkage, or

incorporation of 2'-O-methyl, 2'-O-methyl 3' phosphorothioate, or 2'-O-methyl 3'thioPACE at one or more terminal nucleotides.

19. A composition according to Claim 1, in which the target sequence is adjacent to a T-rich PAM.

20. A composition according to Claim 19, in which the Type-V Cas protein is FnCpf1 and the PAM is TTN, where N is A, C, G or T; or in which the Type-V Cas protein is AsCpf1 or LbCpf1 and the PAM sequence is TTTV, where V is A, C or G.

21. A composition according to Claim 1, in which the CRISPR complex generates a strand break at the target sequence.

22. A composition according to Claim 21, in which the strand break is a staggered double-stranded break with a 5' overhang.

23. A composition according to Claim 21, in which the strand break is a staggered double-stranded break with a 4-nt or 5-nt overhang.

24. A composition according to Claim 21, in which the composition further comprises a single-stranded oligodeoxynucleotide as a template for homology-directed repair of the double-stranded break.

25. A composition according to Claim 21, in which the composition further comprises a double-stranded oligodeoxynucleotide for insertion into the double-stranded break.

26. An *in vitro* or *ex vivo* method for modifying an eukaryotic cell, comprising delivering a composition according to any preceding claim to the eukaryotic cell, in which the target sequence adjacent to the PAM in the genome of the eukaryotic cell is modified by the CRISPR complex formed by the Type-V Cas protein and the Type-V CRISPR-Cas system guide, in which the eukaryotic cell is not a human germline cell.

27. A method according to Claim 26, in which the eukaryotic cell is a mammalian cell or a plant cell.

28. A method according to Claim 27, in which the eukaryotic cell is a human cell.

29. A method according to Claim 28, in which the eukaryotic cell is a hematopoietic cell or a lymphocyte.

30. A method according to Claim 29, in which the eukaryotic cell is a hematopoietic CD34+ stem/progenitor cell, a natural killer cell, a cytotoxic T lymphocyte, a regulatory T lymphocyte, or a tumor-infiltrating lymphocyte.

31. Use of a composition according to any of Claims 1 to 25 in the manufacture of a medicament for treatment of a genetic disease or disorder.

32. Use according to Claim 31, in which the genetic disease or disorder is a blood disease or disorder.

33. Use according to Claim 32, in which the blood disease or disorder is Sickle Cell Anemia, Beta-Thalassemia, or Hemophilia.

34. Use according to Claim 31, in which the genetic disease or disorder is an ophthalmic or ocular disease or disorder.

35. Use according to Claim 34, in which the ophthalmic or ocular disease or disorder is Leber Congenital Amaurosis, Usher Syndrome, Retinitis Pigmentosa, or Primary Open Angle Glaucoma.

36. Use according to Claim 31, in which the genetic disease or disorder is a muscle disease or disorder.

37. Use according to Claim 36, in which the muscle disease or disorder is Cystic Fibrosis or Duchenne Muscular Dystrophy.

38. Use according to Claim 31, in which the genetic disease or disorder is cancer.

39. Use according to Claim 38, in which the Type-V CRISPR-Cas system guide hybridizes with a target sequence associated with PD1, CTLA4, TRAC, TRBC, B2M, or MHC2TA.