CLAIMS

1. A non-naturally occurring nuclease system comprising one or more vectors comprising:

a) a promoter selected from the group consisting of 7sk, SRP-RPS29, SNAR-G-l-CGBl, SNAR- CGB2, RMRP-CCDC 107, tRNA(Lys)-ALOXE3, RNU6-9-MED16: tRNA (Gly)-DPP9, RNU6-2-THEM259, SNORD13-C8orf41, mouse RPPH1-PARP2, rat RPPH1-PARP2, and those RPPH1-PARP2 promoters derived from *ailuropoda melanoleuca, bos taurus, callithrix jacchus, canis familiaris, cavia porcellus, chlorocebus sabaeus, choloepus hoffinanni, dasypus novemcinctus, dipodomys ordii, equus caballus, erinaceus europaeus, felis catus, gorilla gorilla, homo sapiens, ictidomys tridecemlineatus, loxodonta africana, macaca mulatta, mus musculus, mustela putorius furo, myotis lucifugus, nomascus leucogenys, ochotona princeps, oryctolagus cuniculus, otolemur garnettii, ovis aries, pan troglodytes, papio anubis, pongo abelii, procavia capensis, pteropus vampyrus, rattus norvegicus, sus scrofa, tarsius syrichta, tupaia belangeri, tursiops truncatus, vicugna pacos* operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of a DNA molecule or RNA molecule in a cell; and

b) a regulatory element operable in a cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

wherein components (a) and (b) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or both strands of the DNA molecule or RNA molecule.

2. The system of claim 1, wherein the system is CRISPR.

3. The system of claim 1, wherein the system is packaged into a single adeno-associated virus (AAV) particle.

4. The system of claim 1, wherein the system inactivates one or more gene products.

5. The system of claim 1, wherein the nuclease system excises at least one gene mutation.

6. The system of claim 1, further comprising a donor template.

7. The system of claim 2, wherein the nucleotide sequence encoding the genome-targeted nuclease encodes a CRISPR enzyme that is mutated to lack the ability to cleave one or both strands of the target polynucleotide.

8. The system of claim 1, further comprising at least one Kozak sequence.

9. The system of claim 1, further comprising an RNA sequence that mediates cap-independent initiation of translation.

10. The system of claim 1, wherein the promoter is a 7sk promoter selected from the group consisting of 7skl, 7sk2, and 7sk3.

11. The system of claim 10, wherein the 7skl, 7sk2, or 7sk3 promoter is derived from human or mouse.

12. The system of claim 10, wherein the 7skl, 7sk2, or 7sk3 promoter comprises a nucleotide sequence having at least 80% identity to the nucleotide sequence set forth in SEQ ID NOs: 3-8.

13. A non-naturally occurring nuclease system comprising one or more vectors comprising:

a) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of a DNA molecule or RNA molecule in a cell; and

b) a regulatory element operable in a cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

wherein components (a) and (b) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or both strands of the DNA molecule , wherein the promoter comprises at least one modification comprising an element that allows conditional regulation or autoregulation.

14. The system of claim 13, wherein the element is a tet-responsive promoter.

15. The system of claim 14, wherein the tet-responsive promoter comprises a Tet repressor (TetR) and Tet operator (TetO) engineered into the promoter.

16. The system of claim 15, wherein:

(a) the TetR comprises an amino acid sequence having at least 80% identity to SEQ ID NO: 14;

(b) the TetO comprises a nucleotide sequence having at least 80% identity to the nucleotide sequence set forth in SEQ ID NO: 11; or

(c) the promoter is H1, and the H1-TetO comprises a nucleotide sequence having at least 80% identity to the nucleotide sequence set forth in SEQ ID NO: 13.

17. The system of claim 13, wherein the auto-regulation site comprises a nucleotide sequence having at least 80% identity to the nucleotide sequence set forth in SEQ ID NO: 33 or 34.

18. A non-naturally occurring nuclease system comprising one or more vectors comprising:

a) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of a DNA molecule or RNA molecule in a cell; and

b) a regulatory element operable in a cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

wherein components (a) and (b) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or both strands of the DNA molecule or RNA molecule, wherein

the nucleotide sequence of the genome-targeted nuclease comprises is modified to alter the stability of the encoded genome targeted nuclease by

i) fusing a 2A peptide to the nuclease,

ii) fusing a ubiquitin protein to the nuclease, or

iii) fusing a region of a protein required for cell-cycle regulation to the nuclease.

19. The system of claim 15, wherein the 2A peptide is selected from the group consisting of T2A, P2A, E2A and F2A, or an amino acid sequence having at least 80% identity to any of the foregoing.

20. The system of claim 18, wherein the protein is selected from the group consisting of APE2, ATR, BRCA1, Chkl, Cdc5, Cdc6, Cdc7, Cdc45, Cdtl, CSA, CSB, Ctfl8, DDB1, DDB2, DNA2,

DUT, Elgl, EndoV, Espl, Exonucleasel, FBH1, FEN1, Geminin, Husl, KNTC2 (DC80), Ku80, Ligasel, Mad2, MBD4, Mcm3, Mcm4, Mcm5, Mcm6, Mcm7, Mcm8, McmlO, MGMT, MLH3, Mms4, MPG, MSH2, Mus81, BS1, NEIL2, EIL3, NTH1, Orel, Orc3, PARP1, PCNA, Pifl, PMS1, PMS2, PNK, Pola pi 80, Pola p70, Pola Sppl (Prim2a), Polb, Pold pl25, Pole Dpb3, Pole Dpb4, Pole Pol2, Poli, Poll, Polm, Psfl, Psf2, Psf3, Radl, Radl8, Rad23A, Rad23B, Rad51, Rad51D, Rad54, Rad6A, RPA34, RPA70, Sccl, Scc3, Sir2, SIRT1 (Sirtuin), TDG, TDP1, TIMELESS, Tin2, Topoisomerase I, Topoisomerase Ilia, Topoisomerase Illb, Ubcl3, UNG, XAB2, XPC, XPF, XPG, Xrcc2, and XRCC4.

21. The system of claim 18, wherein the protein comprises the amino acids from positions 1-110 (hGem(l-l10)) of human Geminin or amino acids having at least 80% identity thereto.

22. The system of claim 18, wherein the protein comprises amino acids from positions 30-120 (hCdtl(30-120)) of human Cdt1 or amino acids having at least 80% identity thereto.

23. The system of claim 18, wherein the ubiquitin fused to the nuclease comprises an amino acid sequence having at least 80% identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 39-58.

24. The system of any preceding claim, wherein the nuclease is a SaCas9 nickase.

25. Use of the non-naturally occurring nuclease system of claim 1 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of retinal dystrophy, corneal dystrophy, microsatellite expansion diseases, and cancer in a subject in need thereof.

26. The non-naturally occurring nuclease system of claim 1 for use in the treatment of a disease selected from the group consisting of retinal dystrophy, corneal dystrophy, microsatellite expansion diseases, and cancer in a subject in need thereof.