CLAIMS

1. A system capable of site-specifically integrating an exogenous nucleic acid into a mammalian cell genome at a desired target site, wherein the system comprises, in a single composition:

(a) a nucleic acid encoding a DNA binding nickase domain linked to a reverse transcriptase domain;

(b) a nucleic acid encoding at least two guide RNAs (gRNAs) comprising, from 3' to 5',

i. a primer binding sequence,

ii. a sequence complementary to one strand of an integration recognition sequence, and

iii. a target binding sequence,

wherein the gRNA is capable of guiding the linked nickase-reverse transcriptase domains to the genomic target site;

(c) nucleic acid encoding an integration enzyme; and

(d) an exogenous nucleic acid linked to a sequence that is an integration cognate of the integration recognition sequence.

2. The system of claim 1, wherein the DNA binding nickase domain is linked to the reverse transcriptase domain by in-frame fusion.

3. The system of claim 1, wherein the DNA binding nickase domain is linked to the reverse transcriptase domain by a linker.

4. The system of claim 3, wherein the linker is a peptide fused in-frame between the nickase and reverse transcriptase domains.

5. The system of claim 1, wherein the linked DNA binding nickase-reverse transcriptase domains are further linked to the integration enzyme.

6. The system of claim 1, wherein the DNA binding nickase domain is

selected from Cas9-D10A, Cas9-H840A, and Cas12a/b nickase.

7. The system of claim 1, wherein the reverse transcriptase domain is selected from the group consisting of Moloney Murine Leukemia Virus (M-MLV) reverse transcriptase domain, transcription xenopolymerase (RTX), avian myeloblastosis virus reverse transcriptase (AMV-RT), and Eubacterium rectale maturase RT.

8. The system of claim 7, wherein the reverse transcriptase domain is a M-MLV reverse transcriptase domain.

9. The system of claim 7, wherein the M-MLV reverse transcriptase domain comprises one or more mutations selected from the group consisting of D200N, T306K, W313F, T330P, and L603W.

10. The system of claim 1, wherein the exogenous nucleic acid is a minicircle, a plasmid, a mRNA, or a linear DNA

11. The system of claim 9, wherein exogenous nucleic acid is a minicircle.

12. The system of claim 11, wherein the minicircle does not comprise a sequence of a bacterial origin.

13. The system of claim 1, wherein the integration enzyme is selected from the group consisting of Dre, Vika, Bxb1, φC31, RDF, FLP, φBT1, R1, R2, R3, R4, RS, TP901-1, A118, φFC1, φC1, MR11, TG1, φ370.1, Wβ, BL3, SPBc, K38, Peaches, Veracruz, Rebeuca, Theia, Benedict, KSSJEB, PattyP, Doom, Scowl, Lockley, Switzer, Bob3, Troube, Abrogate, Anglerfish, Sarfire, SkiPole, ConceptII, Museum, Severus, Airmid, Benedict, Hinder, ICleared, Sheen, Mundrea, BxZ2, φRV, retrotransposases encoded by R2, L1, Tol2 Te1, Tc3, Mariner Rimar 1, Mariner mos-1, and Minos.

14. The system of claim 13, wherein the integration enzyme is Bxb1.

15. The system of claim 13, wherein the integration recognition sequence is an attB sequence, an attP sequence, a Vox sequence, or a FRT sequence.

16. The system of claim 15, wherein the integration recognition sequence is an attB sequence and the integration cognate is an attP sequence.

17. The system of claim 15, wherein the exogenous nucleic acid encodes: a reporter gene;
a degradation tag for programmable knockdown of proteins in the presence of small molecules;
a T-cell receptor (TCR), a chimeric antigen receptor (CAR), an interleukin, a cytokine, or an immune checkpoint gene and the mammalian cell is a T-cell or natural killer (NK) cell;
a beta hemoglobin (HBB) gene and the mammalian cell is a hematopoietic stem cell (HSC);
a metabolic gene; or
a gene involved in an inherited disease or syndrome.

18. The system of claim 1, wherein the exogenous nucleic acid is between 1000 bp and 36,000 bp in length.

19. The system of claim 1, wherein the exogenous nucleic acid is more than 36,000 bp in length.

20. The system of claim 1, wherein the exogenous nucleic acid is less than 1000 bp in length.

21. The system of claim 17, wherein the inherited disease is cystic fibrosis, familial hypercholesterolemia, adenosine deaminase (ADA) deficiency, X-linked SCID (X-SCID), Wiskott-Aldrich syndrome (WAS), hemochromatosis, Tay-Sachs, fragile X syndrome, Huntington's disease, Marfan syndrome, phenylketonuria, or muscular dystrophy.

22. The system of claim 1, further comprising a nicking gRNA.

23. The system of claim 1, wherein a)-d) are introduced into the mammalian cell as an adeno-associated virus (AAV) or an adenovirus (AdV).

24. The system of claim 1, wherein the nucleic acid encoding at least two gRNAs comprises a nucleic acid encoding two gRNAs.

25. The system of claim 1, wherein the composition is *ex vivo* or *in vitro*.