CLAIMS

We claim:

1. A method for editing a target RNA in a host cell, comprising introducing a deaminase-recruiting RNA (dRNA) or a construct comprising a nucleic acid encoding the dRNA into the host cell, wherein:

(1) the dRNA comprises a targeting RNA sequence that is at least partially complementary to the target RNA,

(2) the dRNA is capable of recruiting an adenosine deaminase acting on RNA (ADAR), and

(3) the dRNA is a circular RNA or capable of forming a circular RNA.

2. The method of claim 1, wherein the dRNA further comprises a 3' ligation sequence and a 5' ligation sequence, optionally wherein:

(i) the 3' ligation sequence and the 5' ligation sequence are at least partially complementary to each other; and/or

(ii) the 3' ligation sequence and the 5' ligation sequence are about 20 to about 75 nucleotides in length.

3. The dRNA of claim 1 or 2, wherein the dRNA is a circular RNA. or wherein the dRNA is a linear RNA capable of forming a circular RNA, particularly, wherein the dRNA is a linear RNA capable of forming a circular RNA, the dRNA is circularized by RNA ligase RtcB, optionally wherein the RNA ligase RtcB is expressed endogenously in the host cell.4.The method of any one of claims 1-3, wherein the method comprises introducing a construct comprising a nucleic acid encoding the dRNA into the host cell, particularly, the construct further comprises a 3' twister ribozyme sequence linked to the 3' end of the nucleic acid encoding the dRNA and a 5' twister ribozyme sequence linked to the 5' end of the nucleic acid encoding the dRNA, optionally wherein:

(i) the 3' twister sequence is twister P3 U2A and the 5' twister sequence is twister P1; or

(ii) the 5' twister sequence is twister P3 U2A and the 3' twister sequence is twister P1.

.5. A method for editing a target RNA in a host cell, comprising introducing a deaminase-recruiting RNA (dRNA) or a construct comprising a nucleic acid encoding the dRNA into the host cell, wherein the dRNA comprises:

(1) a targeting RNA sequence that is at least partially complementary to the target RNA and

(2) a small nucleolar RNA (snoRNA) sequence linked to the 3' and/or 5' ends of the targeting RNA sequence;

and wherein the dRNA is capable of recruiting an adenosine deaminase acting on RNA (ADAR).

6. The method of claim 5, wherein:

(i) the dRNA comprises a snoRNA sequence linked to the 5' end of the targeting RNA sequence ("5' snoRNA sequence");

(ii) the dRNA comprises a snoRNA sequence linked to the 3' end of the targeting RNA sequence (3' snoRNA sequence");

(iii) the snoRNA sequence is at least about 70 nucleotides in length;

(iv) the 3' snoRNA sequence comprises the nucleic acid sequence of SEQ ID NO: 1;

(v) the 5' snoRNA sequence comprises the nucleic acid sequence of SEQ ID NO: 2; and/or

(vi) the snoRNA sequence is a C/D Box snoRNA sequence, an H/ACA Box snoRNA sequence, a composite C/D Box and H/ACA Box snoRNA sequence, or an orphan snoRNA sequence.

7. The method of claim 5 or 6, wherein the method comprises introducing a construct comprising a nucleic acid encoding the dRNA into the host cell, particularly, wherein the construct further comprises a promoter operably linked to the nucleic acid encoding the dRNA, wherein the promoter is a polymerase II promoter ("Pol II promoter"), more particularly, wherein the Pol II promoter is a CMV promoter, optionally wherein the CMV promoter comprises the nucleic acid sequence of SEQ ID NO: 3.

.8. A method for editing a target RNA in a host cell, comprising introducing a construct comprising a nucleic acid encoding a deaminase-recruiting RNA (dRNA) into the host cell, wherein:

(1) the dRNA comprises a targeting RNA sequence that is at least partially complementary to the target RNA,

(2) the dRNA is capable of recruiting an adenosine deaminase acting on RNA (ADAR), and

(3) the construct comprises a polymerase II promoter ("Pol II promoter") operably linked to the nucleic acid encoding the dRNA, particularly, wherein the Pol II promoter is a CMV promoter, optionally wherein the CMV promoter comprises the nucleic acid sequence of SEQ ID NO: 3.

9. The method of any one of claims 4 and 7-8, wherein the construct is a viral vector or a plasmid, optionally wherein the construct is an AAV vector.

10. The method of any one of claims 1-9, wherein the ADAR is endogenously expressed by the host cell, optionally wherein the host cell is a T cell.

11. The method of any one of claims 1-10, wherein:

(i) the targeting RNA sequence is more than 50 nucleotides in length, optionally wherein the targeting RNA sequence is about 100 to about 150 nucleotides in length

(ii) the targeting RNA sequence comprises a cytidine, adenosine or uridine directly opposite the target adenosine in the target RNA, optionally wherein the targeting RNA sequence comprises a cytidine mismatch directly opposite the target adenosine in the target RNA, such as wherein the cytidine mismatch is located at least 20 nucleotides away from the 3' end of the targeting RNA sequence, and at least 5 nucleotides away from the 5' end of the targeting RNA sequence;

(iii) the targeting RNA sequence further comprises one or more guanosines each opposite a non-target adenosine in the target RNA;

(iv) the targeting RNA sequence comprises two or more consecutive mismatch nucleotides opposite a non-target adenosine in the target RNA;

(v) the 5' nearest neighbor of the target adenosine in the target RNA is a nucleotide selected from U, C, A and G with the preference U > C≈A > G and the 3' nearest neighbor of the target adenosine in the target RNA is a nucleotide selected from G, C, A and U with the preference G > C > A≈U;

(vi) the target adenosine is in a three-base motif selected from the group consisting of UAG, UAC, UAA, UAU, CAG, CAC, CAA, CAU, AAG, AAC, AAA, AAU, GAG, GAC, GAA

and GAU in the target RNA, optionally wherein the three-base motif is UAG, and wherein the targeting RNA comprises an A directly opposite the uridine in the three-base motif, a cytidine directly opposite the target adenosine, and a cytidine, guanosine or uridine directly opposite the guanosine in the three-base motif; and/or

(vii) the target RNA is an RNA selected from the group consisting of a pre-messenger RNA, a messenger RNA, a ribosomal RNA, a transfer RNA, a long non-coding RNA and a small RNA, optionally wherein the target RNA is a pre-messenger RNA.

12. The method of any one of claims 1-11, further comprising introducing an inhibitor of ADAR3 and/or a stimulator of interferon to the host cell.

13. The method of any one of claims 1-12, comprising introducing a plurality of dRNAs or constructs each targeting a different target RNA.

14. The method of any one of claims 1-13, wherein the efficiency of editing the target RNA is at least 40%.

15. The method of any one of claims 1-14, wherein the construct or the dRNA does not induce immune response.

16. The method of any one of claims 1-15, further comprising introducing an ADAR to the host cell, optionally wherein the ADAR is an ADAR1 comprising an E1008 mutation.

17. The method of any one of claims 1-16, wherein deamination of the target adenosine in the target RNA results in a missense mutation, an early stop codon, aberrant splicing, or alternative splicing in the target RNA, or reversal of a missense mutation, an early stop codon, aberrant splicing, or alternative splicing in the target RNA, optionally wherein deamination of the target adenosine in the target RNA results in point mutation, truncation, elongation and/or misfolding of the protein encoded by the target RNA, or a functional, full-length, correctly-folded and/or wild-type protein by reversal of a missense mutation, an early stop codon, aberrant splicing, or alternative splicing in the target RNA.

18. The method of any one of claims 1-17, wherein the host cell is a eukaryotic cell, optionally wherein the host cell is a mammalian cell, such as wherein the host cell is a human or mouse cell.

19. An edited RNA or a host cell having an edited RNA produced by the method of any one of claims 1-18.

20. A method for treating or preventing a disease or condition in an individual, comprising editing a target RNA associated with the disease or condition in a cell of the individual according to the method of any one of the claims 1-18.

21. The method of claim 20, wherein:

(i) the disease or condition is a hereditary genetic disease or a disease or condition associated with one or more acquired genetic mutations;

(ii) the target RNA has a G to A mutation; and/or

(iii) the disease or condition is a monogenetic or a polygenetic disease or condition.

22. The method of claim 20 or 21, wherein:

(i) the target RNA is *TP53*, and the disease or condition is cancer;

(ii) the target RNA is *IDUA*, and the disease or condition is Mucopolysaccharidosis type I (MPS I);

(iii) the target RNA is *COL3A1*, and the disease or condition is Ehlers-Danlos syndrome;

(iv) the target RNA is *BMPR2*, and the disease or condition is Joubert syndrome;

(v) the target RNA is *FANCC*, and the disease or condition is Fanconi anemia;

(vi) the target RNA is *MYBPC3*, and the disease or condition is primary familial hypertrophic cardiomyopathy; or

(vii) the target RNA is *IL2RG*, and the disease or condition is X-linked severe combined immunodeficiency.

23. A deaminase-recruiting RNA (dRNA) for editing a target RNA comprising a targeting RNA sequence that is at least partially complementary to the target RNA, wherein the dRNA is capable of recruiting an Adenosine Deaminase Acting on RNA (ADAR), and wherein the dRNA is circular or is capable of forming a circular RNA, particularly, wherein the dRNA further comprises a 3' ligation sequence and a 5' ligation sequence, optionally wherein:

(i) the 3' ligation sequence and the 5' ligation sequence are at least partially complementary to each other; and/or

(ii) the 3' ligation sequence and the 5' ligation sequence are about 20 to about 75 nucleotides in length.

24. The dRNA of claim 23, wherein the dRNA is a circular RNA or the dRNA is a linear RNA capable of forming a circular RNA.

25. A construct comprising a nucleic acid encoding the dRNA of any one of claims 23-24, particularly, wherein the construct further comprises a 3' twister ribozyme sequence linked to the 3' end of the nucleic acid encoding the dRNA and a 5' twister ribozyme sequence linked to the 5' end of the nucleic acid encoding the dRNA, optionally wherein:

(i) the 3' twister sequence is twister P3 U2A and the 5' twister sequence is twister P1; or

(ii) the 5' twister sequence is twister P3 U2A and the 3' twister sequence is twister P1.

26. A deaminase-recruiting RNA (dRNA) for editing a target RNA comprising:

(1) a targeting RNA sequence that is at least partially complementary to the target RNA and

(2) a small nucleolar RNA (snoRNA) sequence at the 3' and/or 5' ends of the targeting RNA sequence;

wherein the dRNA is capable of recruiting an adenosine deaminase acting on RNA (ADAR).

27. The dRNA of claim 26, wherein:

(i) the dRNA comprises a snoRNA sequence linked to the 5' end of the targeting RNA sequence ("5' snoRNA sequence");

(ii) the dRNA comprises a snoRNA sequence linked to the 3' end of the targeting RNA sequence (3' snoRNA sequence");

(iii) the snoRNA sequence is at least about 70 nucleotides in length;

(iv) the 3' snoRNA sequence comprises the nucleic acid sequence of SEQ ID NO: 1;

(v) the 5' snoRNA sequence comprises the nucleic acid sequence of SEQ ID NO: 2; and/or

(vi) the snoRNA sequence is a C/D Box snoRNA sequence, an H/ACA Box snoRNA sequence, a composite C/D Box and H/ACA Box snoRNA sequence, or an orphan snoRNA sequence.

28. A construct comprising a nucleic acid encoding a dRNA of claim 26 or 27, particularly, wherein the construct further comprises a promoter operably linked to the nucleic acid encoding the dRNA, more particularly, wherein the promoter is a polymerase II promoter ("Pol II promoter"), wherein the Pol II promoter is a CMV promoter, optionally wherein the CMV promoter comprises the nucleic acid sequence of SEQ ID NO: 3.

29. A construct comprising a nucleic acid encoding a deaminase-recruiting RNA (dRNA) into the host cell, wherein:

(1) the dRNA comprises a targeting RNA sequence that is at least partially complementary to the target RNA,

(2) the dRNA is capable of recruiting an adenosine deaminase acting on RNA (ADAR), and

(3) the construct comprises a polymerase II promoter ("Pol II promoter") operably linked to the nucleic acid encoding the dRNA, particularly, wherein the Pol II promoter is a CMV promoter, optionally wherein the CMV promoter comprises the nucleic acid sequence of SEQ ID NO: 3.

30. The construct of any one of claims 25 and 28-29, wherein the construct is a viral vector or a plasmid, optionally wherein the construct is an AAV vector.

31. The construct or dRNA of any one of claims 23-30, wherein the target RNA is an RNA selected from the group consisting of a pre-messenger RNA, a messenger RNA, a ribosomal RNA, a transfer RNA, a long non-coding RNA and a small RNA.

32. A host cell comprising the construct or dRNA of any one of claims 23-30.

33. A kit for editing a target RNA in a host cell comprising the construct or dRNA of any one of claims 23-30.