THAT WHICH IS CLAIMED:

1. A nucleic acid molecule comprising a polynucleotide encoding an RNA-guided nuclease (RGN) polypeptide, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to any one of SEQ ID NOs: 19, 13, 3, 7, 16, 1, 2, 4-6, 8-12, 14, 15, 17, 18, and 20.

2. The nucleic acid molecule of claim 1, wherein said polynucleotide encoding an RGN polypeptide is:

a) operably linked to a promoter heterologous to said polynucleotide; and/or

b) codon optimized for expression in a eukaryotic cell.

3. The nucleic acid molecule of claim 1 or 2, wherein said RGN polypeptide:

a) is nuclease inactive or is a nickase; and/or

b) comprises one or more nuclear localization signals.

4. The nucleic acid molecule of any one of claims 1-3, wherein the RGN polypeptide is operably fused to a base-editing polypeptide, optionally wherein the base-editing polypeptide is a deaminase.

5. A vector comprising the nucleic acid molecule of any one of claims 1-4.

6. The vector of claim 5, further comprising at least one nucleotide sequence encoding a gRNA capable of hybridizing to the non-target strand of said target sequence.

7. The vector of claim 6, wherein the guide RNA is selected from the group consisting of:

a) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 40; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 61;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 19;

b) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 33; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 54;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 13;

c) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 23; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 44 or nucleotides 19-111 of SEQ ID NO: 1040;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 3;

d) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 27 or nucleotides 1-22 of SEQ ID NO: 1044 or 1045; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 48 or nucleotides 27-96 of SEQ ID NO 1044 or nucleotides 27-95 of SEQ ID NO: 1045;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 7;

e) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 36; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 57;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 16;

f) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 21; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 42;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 1;

g) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 22; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 43;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 2;

h) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 24; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 45;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 4;

i) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 25 or nucleotides 1-17 of SEQ ID NO: 1041 or 1042; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 46 or nucleotides 22-85 of SEQ ID NO: 1041 or 1042;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 5;

j) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 26; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 47 or nucleotides 24-138 of SEQ ID NO: 1043;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 6;

k) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 28; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 49;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 8;

l) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 29; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 50;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 9;

m) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 30; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 51;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 10;

n) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 31; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 52;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 11;

o) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 32; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 53;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 12;

p) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 34; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 55;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 14;

q) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 35; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 56;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 15;

r) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 37; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 58;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 17;

s) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 38 or 39; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 59 or 60;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 18; and

t) a guide RNA comprising:

i) a CRISPR RNA comprising a CRISPR repeat sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 41; and

ii) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 62;

wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 20.

8. The vector of claim 6 or 7, where said gRNA is a single guide RNA or a dual-guide RNA.

9. An RNA-guided nuclease (RGN) polypeptide, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to any one of SEQ ID NOs: 19, 13, 3, 7, 16, 1, 2, 4-6, 8-12, 14, 15, 17, 18, and 20, optionally wherein the RGN polypeptide comprises one or more nuclear localization signals.

10. The RGN polypeptide of claim 9, wherein said RGN polypeptide is capable of binding a target sequence in a target nucleic acid molecule, wherein said target sequence comprises a target strand and a non-target strand, in an RNA-guided sequence specific manner when bound to a guide RNA (gRNA) capable of hybridizing to the non-target strand of said target sequence.

11. The RGN polypeptide of claim 9 or 10, wherein said RGN polypeptide is capable of cleaving said target nucleic acid molecule upon binding, or wherein said RGN polypeptide is nuclease inactive or a nickase.

12. The RGN polypeptide of any one of claims 9-11, wherein the RGN polypeptide is operably fused to a base-editing polypeptide, optionally wherein the base-editing polypeptide is a deaminase.

13. A ribonucleoprotein (RNP) complex comprising the RGN polypeptide of any one of claims 9-12 and a guide RNA bound to the RGN polypeptide.

14. A nucleic acid molecule comprising a CRISPR RNA (crRNA) or a polynucleotide encoding a crRNA, wherein said crRNA comprises a spacer and a CRISPR repeat, wherein said CRISPR repeat comprises a nucleotide sequence having at least 90%, at least 95%, or 100% sequence identity to any one of SEQ ID NOs: 40; 33; 23; 27 or nucleotides 1-22 of SEQ ID NO: 1044 or 1045; 36; 21; 22; 24; 25 or nucleotides 1-17 of SEQ ID NO: 1041 or 1042; 26; 28; 29; 30; 31; 32; 34; 35; 37, 38 or 39; and 41.

15. The nucleic acid molecule of claim 14, wherein a guide RNA comprising:

a) said crRNA; and

b) a trans-activating CRISPR RNA (tracrRNA) hybridized to said CRISPR repeat of said crRNA;

is capable of hybridizing to the non-target strand of a target sequence in a target nucleic acid molecule in a sequence specific manner through the spacer of said crRNA when said guide RNA is bound to an RNA-guided nuclease (RGN) polypeptide.

16. The nucleic acid molecule of claim 14 or 15, wherein said polynucleotide encoding a crRNA is operably linked to a promoter heterologous to said polynucleotide.

17. A vector comprising the nucleic acid molecule comprising said polynucleotide encoding said crRNA of any one of claims 14-16.

18. The vector of claim 17, wherein said vector further comprises a polynucleotide encoding said tracrRNA.

19. The vector of claim 18, wherein said tracrRNA is selected from the group consisting of:

a) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 61, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 40;

b) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 54, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 33;

c) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 44 or nucleotides 19-111 of SEQ ID NO: 1040, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 23;

d) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 48 or nucleotides 27-96 of SEQ ID NO 1044 or nucleotides 27-95 of SEQ ID NO: 1045, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 27 or nucleotides 1-22 of SEQ ID NO: 1044 or 1045;

e) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 57, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 36;

f) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 42, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 21;

g) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 43, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 22;

h) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 45, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 24;

i) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 46 or nucleotides 22-85 of SEQ ID NO: 1041 or 1042, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 25 or nucleotides 1-17 of SEQ ID NO: 1041 or 1042;

j) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 47 or nucleotides 24-138 of SEQ ID NO: 1043, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 26;

k) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 49, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 28;

l) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 50, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 29;

m) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 51, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 30;

n) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 52, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 31;

o) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 53, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 32;

p) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 55, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 34;

q) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 56, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 35;

r) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 58, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 37;

s) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 59 or 60, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 38 or 39; and

t) a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 62, wherein said CRISPR repeat has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 41.

20. A nucleic acid molecule comprising a trans-activating CRISPR RNA (tracrRNA) or a polynucleotide encoding a tracrRNA comprising a nucleotide sequence having at least 90%, at least 95%, or 100% sequence identity to any one of SEQ ID NOs: 61; 54; 44 or nucleotides 19-111 of SEQ ID NO: 1040; 48 or nucleotides 27-96 of SEQ ID NO: 1044 or nucleotides 27-95 of SEQ ID NO: 1045; 57; 42; 43; 45; 46 or nucleotides 22-85 of SEQ ID NO: 1041 or 1042; 47 or nucleotides 24-138 of SEQ ID NO: 1043; 49; 50; 51; 52; 53; 55; 56; 58; 59 or 60; and 62.

21. The nucleic acid molecule of claim 20, wherein a guide RNA comprising:

a) said tracrRNA; and

b) a crRNA comprising a spacer and a CRISPR repeat, wherein said tracrRNA hybridizes with said CRISPR repeat of said crRNA;

is capable of hybridizing to the non-target strand of a target sequence in a target nucleic acid molecule in a sequence specific manner through the spacer of said crRNA when said guide RNA is bound to an RNA-guided nuclease (RGN) polypeptide.

22. The nucleic acid molecule of claim 20 or 21, wherein said polynucleotide encoding a tracrRNA is operably linked to a promoter heterologous to said polynucleotide.

23. A vector comprising the nucleic acid molecule comprising said polynucleotide encoding said tracrRNA of any one of claims 20-22.

24. The vector of claim 23, wherein said vector further comprises a polynucleotide encoding said crRNA.

25. The vector of claim 24, wherein said crRNA comprises a CRISPR repeat selected from the group consisting of:

a) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 40, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 61;

b) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 33, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 54;

c) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 23, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 44 or nucleotides 19-111 of SEQ ID NO: 1040;

d) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 27 or nucleotides 1-22 of SEQ ID NO: 1044 or 1045, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 48 or nucleotides 27-96 of SEQ ID NO 1044 or nucleotides 27-95 of SEQ ID NO: 1045;

e) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 36, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 57;

f) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 21, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 42;

g) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 22, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 43;

h) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 24, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 45;

i) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 25 or nucleotides 1-17 of SEQ ID NO: 1041 or 1042, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 46 or nucleotides 22-85 of SEQ ID NO: 1041 or 1042;

j) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 26, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 47 or nucleotides 24-138 of SEQ ID NO: 1043;

k) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 28, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 49;

l) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 29, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 50;

m) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 30, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 51;

n) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 31, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 52;

o) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 32, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 53;

p) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 34, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 55;

q) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 35, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 56;

r) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 37, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 58;

s) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 38 or 39, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 59 or 60; and

t) a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 41, wherein said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 62.

26. The vector of any one of claims 17-19 and 23-25, wherein said vector further comprises a polynucleotide encoding said RGN polypeptide.

27. The vector of claim 26, wherein said RGN polypeptide is selected from the group consisting of:

a) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 19, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 40 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 61;

b) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 13, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 33 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 54;

c) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 3, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 23 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 44 or nucleotides 19-111 of SEQ ID NO: 1040;

d) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 7, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 27 or nucleotides 1-22 of SEQ ID NO: 1044 or 1045, and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 48 or nucleotides 27-96 of SEQ ID NO 1044 or nucleotides 27-95 of SEQ ID NO: 1045;

e) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 16, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 36 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 57;

f) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 1, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 21 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 42;

g) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 2, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 22 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 43;

h) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 4, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 24 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 45;

i) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 5, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 25 or nucleotides 1-17 of SEQ ID NO: 1041 or 1042, and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 46 or nucleotides 22-85 of SEQ ID NO: 1041 or 1042;

j) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 6, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 26 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 47 or nucleotides 24-138 of SEQ ID NO: 1043;

k) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 8, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 28 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 49;

l) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 9, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 29 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 50;

m) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 10, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 30 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 51;

n) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 11, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 31 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 52;

o) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 12, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 32 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 53;

p) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 14, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 34 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 55;

q) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 15, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 35 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 56;

r) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 17, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 37 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 58;

s) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 18, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 38, or 39 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 59 or 60; and

t) a RGN polypeptide having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 20, wherein said crRNA comprises a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 41 and said tracrRNA has at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 62.

28. A single guide RNA comprising the nucleic acid molecule comprising said crRNA of any one of claims 14-16 and the nucleic acid molecule comprising said tracrRNA of any one of claims 20-22.

29. A dual guide RNA comprising the nucleic acid molecule comprising said crRNA of any one of claims 14-16 and the nucleic acid molecule comprising said tracrRNA of any one of claims 20-22.

30. A system for binding a target sequence in a target nucleic acid molecule, wherein said target sequence comprises a target strand and a non-target strand, said system comprising:

a) one or more guide RNAs capable of hybridizing to the non-target strand of said target sequence or one or more polynucleotides comprising one or more nucleotide sequences encoding the one or more guide RNAs (gRNAs); and

b) an RNA-guided nuclease (RGN) polypeptide comprising an amino acid sequence having at least 90% sequence, at least 95%, or 100% identity to any one of SEQ ID NOs: 19, 13, 3, 7, 16, 1, 2, 4-6, 8-12, 14, 15, 17, 18, and 20, or a polynucleotide comprising a nucleotide sequence encoding the RGN polypeptide, optionally wherein said RGN polypeptide comprises one or more nuclear localization signals.

31. The system of claim 30, wherein the one or more guide RNAs are capable of forming a complex with the RGN polypeptide in order to direct said RGN polypeptide to bind to said target sequence.

32. The system of claim 30 or 31, wherein:

a) at least one of said nucleotide sequences encoding the one or more guide RNAs and said nucleotide sequence encoding the RGN polypeptide is operably linked to a promoter heterologous to said nucleotide sequence; and/or

b) said nucleotide sequence encoding the RGN polypeptide is codon optimized for expression in a eukaryotic cell.

33. The system of any one of claims 30-32, wherein said RGN polypeptide and said one or more guide RNAs are not found complexed to one another in nature.

34. The system of any one of claims 30-33, wherein said target sequence is a eukaryotic target sequence.

35. The system of any one of claims 30-34, wherein said gRNA is a single guide RNA (sgRNA) or a dual-guide RNA.

36. The system of any one of claims 30-35, wherein said gRNA is selected from the group consisting of:

a) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 40 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 61, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 19;

b) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 33 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 54, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 13;

c) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 23 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 44 or nucleotides 19-111 of SEQ ID NO: 1040, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 3;

d) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 27 or nucleotides 1-22 of SEQ ID NO: 1044 or 1045, and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 48 or nucleotides 27-96 of SEQ ID NO 1044 or nucleotides 27-95 of SEQ ID NO: 1045, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 7;

e) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 36 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 57, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 16;

f) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 21 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 42, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 1;

g) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 22 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 43, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 2;

h) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 24 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 45, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 4;

i) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 25 or nucleotides 1-17 of SEQ ID NO: 1041 or 1042, and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 46 or nucleotides 22-85 of SEQ ID NO: 1041 or 1042, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 5;

j) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 26 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 47 or nucleotides 24-138 of SEQ ID NO: 1043, wherein said RGN

polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 6;

k) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 28 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 49, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 8;

l) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 29 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 50, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 9;

m) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 30 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 51, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NOs:10;

n) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 31 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 52, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 11;

o) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 32 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 53, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 12;

p) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 34 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 55, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 14;

q) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 35 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 56, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 15;

r) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 37 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 58, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 17;

s) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 38 or 39 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 59 or 60, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 18; and

t) a gRNA comprising a CRISPR repeat having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 41 and a tracrRNA having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 62, wherein said RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to SEQ ID NO: 20.

37. The system of any one of claims 30-36, wherein the one or more guide RNAs is capable of hybridizing to the non-target strand of said target sequence and the guide RNA is capable of forming a complex with the RGN polypeptide to direct cleavage of the target nucleic acid molecule.

38. The system of any one of claims 30-36, wherein said RGN polypeptide is nuclease inactive or is a nickase.

39. The system of any one of claims 30-38, wherein the RGN polypeptide is operably linked to a base-editing polypeptide, optionally wherein the base-editing polypeptide is a deaminase.

40. The system of any one of claims 30-39, wherein said system further comprises one or more donor polynucleotides.

41. A cell comprising the nucleic acid molecule of any one of claims 1-4, 14-16, and 20-22, the vector of any one of claims 5-9, 17-19, and 23-27, the single guide RNA of claim 28, the dual guide RNA of claim 29, or the system of any one of claims 30-40.

42. A pharmaceutical composition comprising the nucleic acid molecule of any one of claims 1-4, 14-16, and 20-22, the vector of any one of claims 5-9, 17-19, and 23-27, the cell of claim 41, the RGN polypeptide of any one of claims 9-12, the RNP complex of claim 13, or the system of any one of claims 30-40, and a pharmaceutically acceptable carrier.

43. An *in vitro* or *ex vivo* method for binding a target sequence in a target nucleic acid molecule, wherein the target sequence comprises a target strand and a non-target strand, comprising:
A) delivering a system according to any one of claims 30-40, to said target sequence or a cell comprising the target sequence; or
B) i) assembling an RNA-guided nuclease (RGN) ribonucleotide complex by combining:

a) one or more guide RNAs capable of hybridizing to the non-target strand of the target sequence; and

b) an RGN polypeptide of any one of claims 9-12;

under conditions suitable for formation of the RGN ribonucleotide complex; and

ii) contacting said target nucleic acid molecule or a cell comprising said target nucleic acid molecule with the assembled RGN ribonucleotide complex; wherein the one or more guide RNAs hybridize to the non-target strand of the target sequence, thereby directing said RGN polypeptide to bind to said target sequence.

44. The *in vitro* or *ex vivo* method of claim 43, wherein said RGN polypeptide or said guide RNA further comprises:

a) a detectable label, thereby allowing for detection of said target sequence; and/or

b) an expression modulator, thereby modulating expression of a target gene comprising said target sequence.

45. The *in vitro* or *ex vivo* method of claim 43 or 44, wherein said RGN polypeptide further comprises a base-editing polypeptide, thereby allowing for the modification of said target nucleic acid molecule, optionally wherein said base-editing polypeptide comprises a deaminase.

46. The *in vitro* or *ex vivo* method of claim 43 or 44, wherein said RGN polypeptide is capable of cleaving said target nucleic acid molecule, thereby allowing for the cleaving and/or modifying of said target nucleic acid molecule.

47. An *in vitro* or *ex vivo* method for cleaving and/or modifying a target nucleic acid molecule comprising a target sequence, wherein said target sequence comprises a target strand and a non-target strand, said method comprising:

A) delivering a system according to any one of claims 30-40 to said target sequence or a cell comprising the target sequence, wherein cleavage or modification of said target nucleic acid molecule occurs; or

B) contacting the target nucleic acid molecule with:

i) the RGN polypeptide of any one of claims 9-12; and

ii) one or more guide RNAs capable of targeting the RGN of (i) to the target sequence; wherein the one or more guide RNAs hybridize to the non-target strand of the target sequence, thereby directing said RGN polypeptide to bind to said target nucleic acid molecule and cleavage and/or modification of said target nucleic acid molecule occurs.

48. The *in vitro* or *ex vivo* method of claim 47, wherein said modified target nucleic acid molecule comprises

a) insertion of heterologous DNA into the target nucleic acid molecule;

b) deletion of at least one nucleotide from the target nucleic acid molecule; and/or

c) mutation of at least one nucleotide in the target nucleic acid molecule.

49. The *in vitro* or *ex vivo* method of claim 48, wherein cleavage by said RGN polypeptide generates a double-stranded break or a single-stranded break.

50. The *in vitro* or *ex vivo* method of claim 48, wherein said RGN polypeptide is nuclease inactive or a nickase and is operably fused to a base-editing polypeptide, optionally wherein the base-editing polypeptide is a deaminase.

51. The *in vitro* or *ex vivo* method of any one of claims 43-50, wherein said target sequence is:

a) located adjacent to a protospacer adjacent motif (PAM);

b) a eukaryotic target sequence; and/or

c) within a cell.

52. The *in vitro* or *ex vivo* method of claim 51, wherein said target sequence is within a cell, and wherein said *in vitro* or *ex vivo* method further comprises culturing the cell under conditions in which the RGN polypeptide is expressed and cleaves and modifies the target nucleic acid molecule to produce a DNA molecule comprising a modified target nucleic acid molecule; and selecting a cell comprising said modified target nucleic acid molecule.

53. An *in vitro* or *ex vivo* method for producing a genetically modified cell with a correction in a causal mutation for a genetically inherited disease, the method comprising introducing into the cell:

a) an RNA-guided nuclease (RGN) polypeptide, wherein the RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to any one of SEQ ID NOs: 19, 13, 3, 7, 16, 1, 2, 4-6, 8-12, 14, 15, 17, 18, and 20, or a polynucleotide encoding said RGN polypeptide, wherein said polynucleotide encoding the RGN polypeptide is operably linked to a promoter to enable expression of the RGN polypeptide in the cell; and

b) a guide RNA (gRNA) or a polynucleotide encoding said gRNA, wherein said polynucleotide encoding the gRNA is operably linked to a promoter to enable expression of the gRNA in the cell

whereby the RGN and gRNA target to the genomic location of the causal mutation and modify the genomic sequence to correct the causal mutation.

54. The *in vitro* or *ex vivo* method of claim 53, wherein the RGN is nuclease inactive or a nickase.

55. The *in vitro* or *ex vivo* method of claim 53 or 54, wherein said RGN polypeptide is fused to a base-editing polypeptide, optionally wherein the base-editing polypeptide is a deaminase.

56. The method of any one of claims 53-55, wherein the genetically inherited disease is caused by a single nucleotide polymorphism, and wherein the gRNA further comprises a spacer that targets a region proximal to the causal single nucleotide polymorphism.

57. An *in vitro* or *ex vivo* method for producing a genetically modified cell with a deletion in a disease-causing expanded trinucleotide repeat, the method comprising introducing into the cell:

a) an RNA-guided nuclease (RGN) polypeptide, wherein the RGN polypeptide comprises an amino acid sequence having at least 90%, at least 95%, or 100% sequence identity to any one of SEQ ID NOs: 19, 13, 3, 7, 16, 1, 2, 4-6, 8-12, 14, 15, 17, 18, and 20, or a polynucleotide encoding said RGN polypeptide, wherein said polynucleotide encoding the RGN polypeptide is operably linked to a promoter to enable expression of the RGN polypeptide in the cell; and

b) a first guide RNA (gRNA), or a polynucleotide encoding said first gRNA, wherein said polynucleotide encoding the first gRNA is operably linked to a promoter to enable expression of the first gRNA in the cell, and further wherein the first gRNA comprises a spacer that targets the 5' flank of the expanded trinucleotide repeat; and

c) a second guide RNA (gRNA), or a polynucleotide encoding said second gRNA, wherein said polynucleotide encoding the second gRNA is operably linked to a promoter to enable expression of the second gRNA in the cell, and further wherein said second gRNA comprises a spacer that targets the 3'flank of the expanded trinucleotide repeat;

whereby the RGN and the two gRNAs target to the expanded trinucleotide repeat and at least a portion of the expanded trinucleotide repeat is removed.

58. The *in vitro* or *ex vivo* method of claim 57, wherein the first gRNA and/or the second gRNA further comprises a spacer that targets a region within or proximal to the expanded trinucleotide repeat.

59. The nucleic acid molecule of any one of claims 1-4, 14-16, and 20-22, the vector of any one of claims 5-9, 17-19, and 23-27, the cell of claim 41, the RGN polypeptide of any one of claims 9-12, the RNP complex of claim 13, or the system of any one of claims 30-40 for use as a medicament.