CLAIMS

What is claimed is:

1. A composition comprising a nucleic acid sequence encoding an RNA-binding polypeptide comprising a non-guided RNA binding polypeptide or a guided RNA-binding polypeptide capable of binding a toxic target CAG repeat RNA sequence.
2. The composition of claim 1, wherein the RNA-binding polypeptide is a fusion protein.
3. The composition of claim 2, wherein the fusion protein comprises the RNA binding polypeptide fused to an endonuclease capable of cleaving the toxic CAG repeat RNA sequence.
4. The composition of any one of the preceding claims, wherein the non-guided RNA binding polypeptide is a PUF or PUMBY protein.
5. The composition of any one of the preceding claims, wherein the guided RNA-binding polypeptide is a Cas13d protein.
6. The composition of any one of the preceding claims, wherein the cas13d protein is catalytically dead.
7. The composition of any one of the preceding claims, wherein the cas13d protein comprises an amino acid sequence set forth in any one of SEQ ID NOs 587 or 590-594.
8. The composition of any one of the preceding claims, wherein the endonuclease is a nuclease domain of a ZC3H12A zinc-finger endonuclease.
9. The composition of any one of the preceding claims, wherein the PUF RNA binding protein comprises an amino acid sequence set forth in any one of SEQ ID NOs 444-451, 461, 480-488, 549-557, or 656.
10. The composition of any one of the preceding claims, wherein the toxic target CAG RNA repeat sequence comprises any one of the nucleic acid sequences set forth in SEQ ID NOs 453-456 or 472-479.
11. The composition of any one of the preceding claims, wherein the CAG-targeting PUF protein is encoded by a nucleic acid sequence as set forth in SEQ ID NO: 577, 581, 614, 619, 621, or 622.
12. The composition of any one of the preceding claims, wherein the PUF or PUMBY protein is linked to the ZC3H12A endonuclease by a linker sequence.

13. The composition of any one of the preceding claims, wherein the ZC3H12A zinc finger nuclease comprises the amino acid sequence set forth in SEQ ID NO: 358 or SEQ ID NO: 359.
14. The composition of any one of the preceding claims, wherein the fusion protein comprises the amino acid sequence set forth in any one of SEQ ID NO: 460.
15. The composition of any one of the preceding claims, wherein the fusion protein is encoded by a nucleic acid sequence comprising SEQ ID NO: 574-582.
16. The composition of any one of the preceding claims, wherein the nucleic acid molecule encoding the fusion protein comprises a promoter.
17. The composition of claim 16, wherein the promoter is a tCAG promoter, EFS/UBB promoter, or synapsin promoter.
18. An AAV vector of any one of the preceding claims, wherein the AAV vector comprises:
    a first AAV ITR sequence;
    a first promoter sequence;
    a polynucleotide sequence encoding for at least one CAG-repeat RNA binding polypeptide; and
    a second AAV ITR sequence.
19. The AAV vector of any one of the preceding claims, wherein the CAG-repeat RNA binding polypeptide comprises a PUF or PUMBY protein.
20. The AAV vector of any one of the preceding claims, wherein the first AAV ITR sequence or the second AAV ITR sequence comprises a nucleic acid sequence set forth in SEQ ID NO: 597 or 598.
21. The AAV vector of any one of the preceding claims, wherein the vector is encoded be a nucleic set forth in any of one of SEQ ID NO: 588, 589, 624, or 625.
22. An AAV viral vector comprising:
    a) an AAV vector of any one of the preceding claims; and
    b) an AAV capsid protein.
23. The AAV viral vector of claim 22, wherein the AAV capsid protein is an AAV1 capsid protein, an AAV2 capsid protein, an AAV4 capsid protein, an AAV5 capsid protein, an AAV6 capsid protein, an AAV7 capsid protein, an AAV8 capsid protein, an AAV9 capsid protein, an AAV10 capsid protein, an AAV11 capsid protein, an AAV12 capsid protein, an AAV13 capsid protein, an AAVPHP.B capsid

protein, an AAVrh74 capsid protein or an AAVrh.10 capsid protein.

24. A cell comprising the vector of any one of the preceding claims.

25. Use of the composition according to any one of claims 1-17 or the AAV vector according to any one of claims 18-23 in the manufacture of a medicament for treating a CAG repeat disease in a mammal, wherein the composition or the AAV vector is to be administered to a toxic target CAG microsatellite repeat expansion (MRE) RNA sequence in tissues of the mammal whereby the level of expression of the toxic target RNA is to be reduced.

26. The use of claim 25, wherein the composition or AAV vector is to be administered to the subject intravenously, intrathecally, intracerebrally, intraventricularly, intranasally, intratracheally, intra-aurally, intra-ocularly, or peri-ocularly, orally, rectally, transmucosally, inhalationally, transdermally, parenterally, subcutaneously, intradermally, intramuscularly, intracisternally, intranervally, intrapleurally, topically, intralymphatically, intracisternally or intranerve.

27. The use of claim 25, wherein the CAG repeat disorder is Huntington's Disease (HD) or Spinocerebellar Ataxia Type 1 (SCA1).

28. The use of claim 25, wherein the reduced level of expression of the toxic target RNA thereby ameliorates symptoms of HD or SCA1 in the mammal.

29. The use of claim 25, wherein the level of expression of the toxic target RNA is to be reduced compared to the reduction in the level of expression of untreated toxic target CAG RNA.

30. The composition according to any one of claims 1-17 or the AAV viral vector according to any one of claims 18-23 for use as a medicament.