CLAIMS

1. A U1 adaptor oligonucleotide comprising a nucleic acid molecule comprising an annealing domain operably linked to an effector domain, wherein said annealing domain hybridizes to the pre-mRNA of the full length huntingtin (HTT) gene, and wherein said effector domain hybridizes to the U1 snRNA of U1 snRNP.

2. The U1 adaptor oligonucleotide of claim 1, wherein said annealing domain is about 10 to about 30 nucleotides in length.

3. The U1 adaptor oligonucleotide of claim 1, wherein said effector domain is about 8 to about 20 nucleotides in length.

4. The U1 adaptor oligonucleotide of claim 1, wherein said effector domain and said annealing domain are linked by a bond or a linker domain of about 1 to about 10 nucleotides.

5. The U1 adaptor oligonucleotide of claim 1, wherein the nucleic acid sequence of said effector domain comprises the nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 4, or SEQ ID NO: 5, wherein uracil bases and thymidine bases may be exchanged.

6. The U1 adaptor oligonucleotide of claim 5, wherein the nucleic acid sequence of said effector domain comprises the nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 4, or SEQ ID NO: 5.

7. The U1 adaptor oligonucleotide of claim 1, further comprising a first targeting moiety operably linked to said U1 adaptor oligonucleotide.

8. The U1 adaptor oligonucleotide of claim 1, wherein the nucleic acid sequence of said U1 adaptor oligonucleotide comprises at least one nucleotide analog.

9. The U1 adaptor oligonucleotide of claim 1, wherein the nucleic acid sequence of said U1 adaptor oligonucleotide comprises 2'-O-methyl nucleotides, 2'-O-methyloxyethoxy nucleotides, 2’-halo (e.g., 2’-fluoro), and/or locked nucleic acids.

10. The U1 adaptor oligonucleotide of claim 1, wherein the nucleic acid sequence of said U1 adaptor oligonucleotide comprises phosphorothioates.

11. The U1 adaptor oligonucleotide of claim 1, wherein said annealing domain hybridizes with a target sequence in the 3' terminal exon of the HTT gene.

12. The U1 adaptor oligonucleotide of claim 1, wherein the effector domain is operably linked to the 3' end of the annealing domain, the 5' end of the annealing domain, or both the 5' and 3' end of said annealing domain.

13. The U1 adaptor oligonucleotide of claim 1, wherein said U1 snRNA is a U1 variant snRNA.

14. The U1 adaptor oligonucleotide of claim 7, wherein said U1 adaptor oligonucleotide and said first targeting moiety are conjugated via a linker.

15. The U1 adaptor oligonucleotide of claim 14, wherein said linker is cleavable.

16. The U1 adaptor oligonucleotide of claim 7, wherein said first targeting moiety is operably linked to the 3' end, the 5' end, or both the 5' and 3' end of said U1 adaptor oligonucleotide.

17. The U1 adaptor oligonucleotide of claim 16, wherein said first targeting moiety is operably linked to the 5' end of the U1 adaptor oligonucleotide.

18. The U1 adaptor oligonucleotide of claim 7, comprising a second targeting moiety operably linked to said U1 adaptor oligonucleotide, wherein said first targeting moiety is operably linked at the 3' end of said U1 adaptor oligonucleotide and said second targeting moiety is operably linked at the 5'end of said U1 adaptor oligonucleotide.

19. The U1 adaptor oligonucleotide of claim 7, wherein said first targeting moiety is an antibody or functional fragment thereof.

20. The U1 adaptor oligonucleotide of claim 1, wherein said U1 adaptor oligonucleotide comprises the nucleic acid sequence of any one of SEQ ID NO: 8, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID

NO: 9, SEQ ID NO: 39, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or SEQ ID NO: 16, wherein uracil bases and thymidine bases may be exchanged.

21. The U1 adaptor oligonucleotide of claim 20, wherein said U1 adaptor oligonucleotide comprises the nucleic acid sequence of any one of SEQ ID NO: 8, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 9, SEQ ID NO: 39, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or SEQ ID NO: 16.

22. The U1 adaptor oligonucleotide of claim 21, wherein said U1 adaptor oligonucleotide comprises the nucleic acid sequence of any one of SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 15.

23. The U1 adaptor oligonucleotide of claim 1, wherein said annealing domain hybridizes with the corresponding RNA nucleic acid sequence to the DNA nucleic acid sequence of any one of SEQ ID NOs: 26-36.

24. The U1 adaptor oligonucleotide of claim 23, wherein said annealing domain hybridizes with the corresponding RNA nucleic acid sequence to the DNA nucleic acid sequence of any one of SEQ ID NO: 26, SEQ ID NO: 29, or SEQ ID NO: 35.

25. The U1 adaptor oligonucleotide of claim 1, wherein said annealing domain comprises a nucleic acid sequence that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 100% complementary to the RNA nucleic acid sequence corresponding to the DNA nucleic acid sequence of any one of SEQ ID NOS: 26-36.

26. The U1 adaptor oligonucleotide of claim 25, wherein said annealing domain comprises an RNA nucleic acid sequence that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 100% complementary to the RNA nucleic acid sequence corresponding to the DNA nucleic acid sequence of any one of SEQ ID NOS: 26-36.

27. The U1 adaptor oligonucleotide of claim 1, wherein said effector domain comprises a nucleic acid sequence that is at least 75%, at least 80%, at least 85%, at least 90%, at least

95%, at least 97%, or at least 100% identical to the nucleic acid sequence of SEQ ID NOS: 1, 4, or 5, wherein uracil bases and thymidine bases may be exchanged.

28. The U1 adaptor oligonucleotide of claim 27, wherein said effector domain comprises a nucleic acid sequence that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 100% identical to the nucleic acid sequence of SEQ ID NOS: 1, 4, or 5.

29. The U1 adaptor oligonucleotide of claim 1, wherein the U1 adaptor oligonucleotide comprises a nucleic acid sequence that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 100% identical to the nucleic acid sequence of SEQ ID NO: 8, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 9, SEQ ID NO: 39, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or SEQ ID NO: 16, wherein uracil bases and thymidine bases may be exchanged.

30. The U1 adaptor oligonucleotide of claim 29, wherein the U1 adaptor oligonucleotide comprises a nucleic acid sequence that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 100% identical to the nucleic acid sequence of SEQ ID NO: 8, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 9, SEQ ID NO: 39, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or SEQ ID NO: 16.

31. The U1 adaptor oligonucleotide of claim 30, wherein the U1 adaptor oligonucleotide comprises a nucleic acid sequence that is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 100% identical to the nucleic acid sequence of SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 15.

32. The U1 adaptor oligonucleotide of claim 1, wherein the U1 adaptor oligonucleotide comprises the sequence of any one of SEQ ID NOS: 356-680, wherein uracil bases and thymidine bases may be exchanged

33. The U1 adaptor oligonucleotide of claim 32, wherein the U1 adaptor oligonucleotide comprises the sequence of any one of SEQ ID NOS: 356-680, wherein uracil bases and thymidine bases are exchanged.

34. The U1 adaptor oligonucleotide of claim 1, wherein said annealing domain hybridizes with the corresponding RNA nucleic acid sequence of the DNA nucleic acid sequence of any one of SEQ ID NOS: 40-355.

35. The U1 adaptor oligonucleotide of claim 7, wherein said first targeting moiety is an antibody or functional fragment thereof that specifically binds a surface protein on a target cell.

36. The U1 adaptor oligonucleotide of claim 7, wherein said first targeting moiety is Fab, Fab', F(ab')2, F(v), scFv, scFv2, and scFv-Fc.

37. The U1 adaptor oligonucleotide of claim 1, further comprising at least one cell penetrating moiety that is operably linked to said U1 adaptor oligonucleotide.

38. The U1 adaptor oligonucleotide of claim 37, wherein said U1 adaptor oligonucleotide and said cell penetrating moiety are conjugated via a linker.

39. The U1 adaptor oligonucleotide of claim 38, wherein said linker is cleavable.

40. The U1 adaptor oligonucleotide of claim 37, wherein said cell penetrating moiety is operably linked to the 3’ end, the 5’ end, or both the 5’ and 3’ end of said U1 adaptor oligonucleotide.

41. A composition comprising at least one U1 adaptor oligonucleotide of any one of claims 1-40 and at least one pharmaceutically acceptable carrier.

42. The composition of claim 41, wherein said composition further comprises at least one siRNA or antisense oligonucleotide directed against said HTT gene.

43. A method of inhibiting the expression of the HTT gene comprising delivering to a cell a first U1 adaptor oligonucleotide of any one of claims 1-40.

44. The method of claim 27, comprising delivering a second U1 adaptor oligonucleotide of any one of claims 1-40, wherein the annealing domain of said first U1 adaptor oligonucleotide hybridizes with a different target sequence in the pre-mRNA of the HTT gene than the annealing domain of said second U1 adaptor oligonucleotide.

45. Use of the U1 adaptor of any one of claims 1-40 for the manufacture of a medicament for the treatment of Huntington's disease in a subject in need thereof.

46. The use according to claim 45, wherein the medicament is for administering said first U1 adaptor oligonucleotide in association with a second U1 adaptor oligonucleotide of any one of claims 1-40, wherein the annealing domain of said first U1 adaptor oligonucleotide hybridizes with a different target sequence in the pre-mRNA of said HTT gene than the annealing domain of said second U1 adaptor oligonucleotide.

47. The use according to claim 45, wherein the medicament is for administering said first U1 adaptor oligonucleotide in association with at least one siRNA or antisense oligonucleotide directed against said HTT gene.