CLAIMS

1. A modulatory polynucleotide comprising

(a) a stem and loop to form a stem-loop structure, the sequence of said stem-loop structure from 5’ to 3’ comprising:

(i) a UG motif at or near the base of the 5’ stem of the stem-loop structure;

(ii) a 5’ stem arm comprising a passenger strand and optional 5’ spacer region,

wherein said 5’ spacer region, when present, is located between said UG motif and said passenger strand;

(iii) a loop region comprising a UGUG motif at the 5’ end of said loop region;

(iii) a 3’ stem arm comprising a guide strand and optionally a 3’ spacer region, wherein a uridine is present at the 5’ end of the guide strand and wherein said 3’ spacer region, when present, has a length sufficient to form one helical turn;

(b) a first flanking region located 5’ to said stem-loop structure; and

(c) a second flanking region located 3’ to said stem-loop structure, said second region comprising a CNNC motif, and wherein said second flanking region is a 3’ flanking region and comprises SEQ ID NO: 11.

2. The modulatory polynucleotide of claim 1, wherein the loop region of said stem-loop structure is derived from a canonical microRNA.

3. The modulatory polynucleotide of claim 2, wherein the canonical microRNA is miR-22.

4. The modulatory polynucleotide of claim 1, wherein the first flanking region is a 5’ flanking region and comprises SEQ ID NO: 2.

5. The modulatory polynucleotide of claim 1, wherein the loop region comprises SEQ ID NO: 5.

6. The modulatory polynucleotide of claim 1, wherein the first flanking region is a 5’ flanking region and comprises a nucleotide sequence which is at least 95% identical to SEQ ID NO: 2.

7. The modulatory polynucleotide of claim 1, wherein the guide strand comprises a microRNA seed sequence between positions 2 and 15.

8. The modulatory polynucleotide of claim 7, wherein the guide strand comprises a microRNA seed sequence at positions 2-7, 2-8 or 2-9.

9. The modulatory polynucleotide of claim 1, wherein the guide strand is from between 15-30 nucleotides in length.

10. The modulatory polynucleotide of claim 9, wherein the passenger strand is at least 70% complementary to the guide strand.

11. The modulatory polynucleotide of claim 9, wherein the guide strand is from between 21-25 nucleotides in length.

12. The modulatory polynucleotide of claim 11, wherein the guide strand is 22 nucleotides in length.

13. The modulatory polynucleotide of claim 11, wherein the guide strand is 21 nucleotides in length.

14. The modulatory polynucleotide of claim 9, wherein the guide strand is at least 70% complementary to a target RNA, said target RNA selected from the group consisting of mammalian coding mRNA and mammalian non-coding RNA.

15. The modulatory polynucleotide of claim 14, wherein the target RNA is a mammalian coding mRNA.

16. The modulatory polynucleotide of claim 15, wherein the coding mRNA is expressed in a neurologic cell, tissue or organ.

17. An artificial pre-microRNA comprising

(a) a stem and loop to form a stem-loop structure, the sequence of said stem-loop structure from 5’ to 3’ comprising:

(i) a 5’ stem arm comprising a passenger strand and a 5’ spacer region, wherein said 5’ spacer region is located 5’ to said passenger strand;

(ii) a loop region comprising a UGUG motif at the 5’ end of said loop region;

(iii) a 3’ stem arm comprising a guide strand and 3’ spacer region, wherein a uridine is present at the 5’ end of the guide strand and wherein said 3’ spacer region has a length sufficient to form one helical turn; and

(iv) optionally, a UG motif at or near the base of the 5’ stem of the stem-loop structure; and

(b) a 3’flanking region located 3’ to said stem-loop structure, wherein said 3’ flanking region comprises SEQ ID NO: 11.

18. An artificial pre-microRNA comprising

(a) a stem and loop to form a stem-loop structure, the sequence of said stem-loop structure from 5’ to 3’ comprising:

(i) a 5’ stem arm comprising a guide strand and a 5’ spacer region, wherein said 5’ spacer region is located 5’ to said guide strand;

(ii) a loop region comprising a UGUG motif at the 5’ end of said loop region;

(iii) a 3’ stem arm comprising a passenger strand and 3’ spacer region, wherein a uridine is present at the 5’ end of the passenger strand and wherein said 3’ spacer region has a length sufficient to form one helical turn; and

(iv) optionally, a UG motif at or near the base of the 5’ stem of the stem-loop structure; and

(b) a 3’flanking region located 3’ to said stem-loop structure, wherein said 3’ flanking region comprises SEQ ID NO: 11.

19. A vector encoding the modulatory polynucleotide of any of claims 1-18.

20. The vector of claim 19 comprising a recombinant adeno-associated viral (AAV) construct.

21. A recombinant AAV virus comprising the AAV construct of claim 20.

22. The recombinant AAV virus of claim 21, comprising an AAV1 capsid serotype.