Claims

1. A therapeutic genetic construct encoding: (a) a first pre-miRNA; (b) a second pre-miRNA; and (c) transgene encoding AAT(M).

2. The genetic construct of claim 1, wherein at least 7 nucleotides separate the nucleic acids encoding the first pre-miRNA and the nucleic acid encoding the second pre-miRNA.

3. The genetic construct of claim 1, wherein the first and second pre-miRNAs each comprise a guide miRNA that inhibits the expression of an allele encoding a mutant variant of alpha-1 antitrypsin (AAT).

4. The genetic construct of claim 3, wherein each guide miRNA inhibits the expression of AAT(Z).

5. The genetic construct of claim 1, wherein the first pre-miRNA comprises backbone segments that are identical to the corresponding backbone segments of miR204 and the second miRNA comprises backbone segments that are identical to the corresponding backbone segments of miR206.

6. The genetic construct of claim 1, wherein the first and second pre-miRNAs are encoded by the nucleic acid of SEQ ID NO: 267.

7. The genetic construct of claim 1, wherein the transgene encoding AAT(M) differs from the wild-type gene encoding AAT(M) by silent mutations that allow it to evade reduction of expression by the pre-miRNAs.

8. The genetic construct of claim 1, wherein the transgene encoding AAT(M) comprises a nucleic acid sequence having at least about 80% sequence identity with SEQ ID NO: 590 or 596.

9. The genetic construct of claim 1, wherein the transgene encoding AAT(M) comprises the nucleic acid sequence of SEQ ID NO: 590.

10. The genetic construct of claim 1, wherein the transgene encoding AAT(M) encodes the amino acid sequence of SEQ ID NO: 600.

11. The genetic construct of claim 1, further comprising a liver-specific promoter.

12. The genetic construct of claim 11, wherein the liver-specific promoter comprises the nucleic acid sequence of SEQ ID NO: 587 or 594.

13. A vector comprising the genetic construct of any one of claims 1–12.

14. The vector of claim 13, wherein the vector is an adenoviral vector lacking portions of or the entire E1 and/or E4 regions.

15. The vector of claim 13, wherein the vector is a gorilla adenoviral vector.

16. The vector of claim 13, wherein the vector is a GC44 gorilla adenoviral vector.

17. The vector of claim 13, comprising the nucleic acid sequence of SEQ ID NO: 593.

18. A use of the genetic construct of any one of claims 1–12 in the manufacture of a medicament for use in treating a disease or disorder in a subject in need thereof.

19. The use of claim 18, wherein the disease or disorder is a liver or lung disease associated with alpha-1 antitrypsin deficiency.

20. A kit comprising the genetic construct of any one of claims 1–12 and instructions for use.