CLAIMS:

1. A bidirectional nucleic acid construct comprising:

a) a first segment comprising a first alpha-1 antitrypsin (AAT) polypeptide coding sequence comprising the nucleic acid sequence of SEQ ID NO: 781; and

b) a second segment comprising a reverse complement of a second AAT polypeptide coding sequence comprising the nucleic acid sequence of SEQ ID NO: 782;

wherein the construct does not comprise a promoter that drives the expression of either the first AAT polypeptide coding sequence or the second AAT polypeptide coding sequence.

2. The bidirectional nucleic acid construct of claim 1, wherein the second segment is 3' of the first segment.

3. The bidirectional nucleic acid construct of claim 1 or claim 2, wherein the construct does not comprise a homology arm.

4. The bidirectional nucleic acid construct of any one of claims 1-3, wherein the first segment is linked to the second segment by a linker.

5. The bidirectional nucleic acid construct of claim 4, wherein the linker is CpG depleted.

6. The bidirectional nucleic acid construct of any one of claims 1-5, wherein each of the first and second segments comprises a polyadenylation tail sequence, a polyadenylation signal sequence, or a polyadenylation site.

7. The bidirectional nucleic acid construct of any of one claims 1-6, wherein the construct comprises a splice acceptor site.

8. The bidirectional construct of claim 7, wherein the splice acceptor site comprises a human splice acceptor site.

9. The bidirectional construct of claim 7, wherein the splice acceptor site comprises a murine splice acceptor site.

10. The bidirectional nucleic acid construct of claim 7, wherein the construct comprises a first splice acceptor site upstream of the first segment and a second (reverse) splice acceptor site downstream of the second segment.

11. The bidirectional nucleic acid construct of any one of claims 1-10, wherein the construct is single-stranded, optionally single-stranded DNA.

12. The bidirectional nucleic acid construct of any one of claims 1-11, wherein the construct comprises one or more of the following terminal structures: hairpin, loops, inverted terminal repeats (ITR), or toroid.

13. The bidirectional nucleic acid construct of claim 12, wherein the terminal structure is CpG depleted.

14. The bidirectional nucleic acid construct of any one of claims 1-13, wherein the construct comprises one, two, or three inverted terminal repeats (ITR).

15. The bidirectional nucleic acid construct of any one of claims 1-14, wherein the nucleic acid sequence of the bidirectional nucleic acid construct comprises SEQ ID NO: 780 or nucleic acids 441-3796 set forth in SEQ ID NO: 780.

16. The bidirectional nucleic acid construct of any one of claims 1-14, wherein the bidirectional construct encodes a polypeptide comprising the sequence of SEQ ID NO: 702.

17. The bidirectional nucleic acid construct of any one of claims 1-16, wherein the bidirectional construct nucleotide sequence is CpG depleted wherein the ITR is not CpG depleted.

18. Use of the bidirectional nucleic acid construct of any one of claims 1-17 in the manufacture of a medicament for treating alpha-1 antitrypsin deficiency (AATD), the medicament comprising:

i) a bidirectional nucleic acid construct of any one of claims 1-17;

ii) an RNA-guided DNA binding agent; and

iii) an albumin guide RNA (gRNA) comprising a sequence chosen from:

a) a sequence that is at least 95% identical to a sequence selected from the group consisting of SEQ ID Nos: 2-33;

b) at least 17, 18, 19, or 20 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 2-33;

c) a sequence selected from the group consisting of SEQ ID NOs: 2-33

wherein the medicament is formulated for administration in a subject.

19. The use of claim 18, wherein:

(a) the medicament increases the subject's level of functional AAT to at least about 500 μg/ml; or

(b) the medicament increases the subject's level of functional AAT by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, as compared to the subject's level of functional AAT before administration.

20. The use of claim 19, wherein the level of functional AAT in the subject is maintained for at least a year following administration.

21. The use of claim 19 or 20, wherein the level of AAT is measured in serum or plasma.

22. The use of any one of claims 18-21, wherein the subject has impaired liver or lung function.

23. The use of any one of claims 18-22, wherein the medicament delays progression of emphysema in the subject.

24. The use of any one of claims 18-23, wherein the medicament further reduces expression of the endogenous *SERPINA1* gene without significantly reducing expression of the AAT polypeptide coding sequences of the bidirectional nucleic acid construct.

25. The use of claim 24, wherein the medicament is formulated for co-administration with an endogenous *SERPINA1* gene targeted nucleic acid therapeutic agent.

26. The use of claim 25, wherein the endogenous *SERPINA1* gene targeted nucleic acid therapeutic agent is an siRNA, a dsRNA, or a guide RNA.

27. The use of claim 26, wherein the endogenous *SERPINA1* gene targeted nucleic acid therapeutic agent is selected from an RNAi agent targeted to nucleotides 957-977, 1403-1425, or 1410-1436 of SEQ ID NO: 703, and a guide RNA targeted the endogenous *SERPINA1* gene at a position corresponding to nucleotides 412-431, 506-525, or 538-557 of SEQ ID NO: 703.

28. The use of any one of claims 24-27, wherein the medicament induces a double-stranded break (DSB) within the endogenous *SERPINA1* gene.

29. The use of claim 28, wherein the medicament induces a double-strand break (DSB) within the endogenous *SERPINA1* gene at a position corresponding to nucleotides 412-431, 506-525, or 538-557 of SEQ ID NO: 703.

30. The use of any one of claims 18-27, wherein the medicament induces modification of the endogenous *SERPINA1* gene.

31. The use of claim any one of claims 28-30, wherein the DSB is induced within the endogenous *SERPINA1* gene or the endogenous *SERPINA1* gene is modified after contacting the cell or population of cells or administering to the subject the bidirectional nucleic acid construct.

32. The use of any one of claims 18-31, wherein the endogenous *SERPINA1* gene targeted nucleic acid agent is a *SERPINA1* guide RNA that is at least partially complementary to a target

sequence present in exon 2, 3, 4, or 5 of the endogenous human *SERPINA1* gene and that targets neither the first AAT polypeptide coding sequence nor the second AAT polypeptide coding sequences.

33. The use of any one of claims 18-31, wherein the endogenous *SERPINA1* gene targeted nucleic acid agent is a *SERPINA1* guide RNA that is at least partially complementary to a target sequence within the endogenous *SERPINA1* gene at a position corresponding to nucleotides 412-431, 506-525, or 538-557 of SEQ ID NO: 703.

34. The use of claim 32 or 33, wherein the *SERPINA1* guide RNA comprises:

a guide sequence selected from SEQ ID NOs: 1129-1131;

a guide sequence that is at least 95% identical to SEQ ID NOs: 1129-1131; or

17, 18, 19, or 20 consecutive nucleotides of a sequence chosen from SEQ ID NOs: 1129-1131.

35. The use of any one of claims 18-34, wherein the medicament is formulated for administration in vivo.

36. The use of any one of claims 18-35, wherein the nucleic acid construct is administered in a nucleic acid vector or a lipid nanoparticle.

37. The use of any one of claims 18-36, wherein

i) the RNA-guided DNA binding agent or albumin gRNA is delivered or administered in a nucleic acid vector or lipid nanoparticle; and/or

ii) the RNA-guided DNA binding agent or *SERPINA1* gRNA is delivered or administered in a nucleic acid vector or lipid nanoparticle.

38. The use of claim 37, wherein the nucleic acid vector is a viral vector selected from the group consisting of an adeno associate viral (AAV) vector, adenovirus vector, retrovirus vector, and lentivirus vector.

39. The use of claim 38, wherein the nucleic acid vector is a AAV vector, and the AAV vector is selected from the group consisting of AAV1, AAV2, AAV3, AAV3B, AAV4, AAV5, AAV6, AAV6.2, AAV7, AAVrh.64R1, AAVhu.37, AAVrh.8, AAVrh.32.33, AAV8, AAV9, AAV-DJ, AAV2/8, AAVrh10, AAVLK03, AV10, AAV11, AAV12, rh10, and hybrids thereof.

40. The use of any one of claims 18-39, wherein the RNA-guided DNA binding agent is a class 2 Cas nuclease.

41. The use of claim 40, wherein the Cas nuclease is a cleavase or a Cas9 nuclease.

42. The use of claim 41, wherein the nucleic acid vector is a Cas9 nuclease and the Cas9 nuclease is an *S. pyogenes* Cas9 nuclease.

43. A vector comprising the bidirectional nucleic acid construct of any one of claims 1-17.

44. The vector of claim 43, wherein the vector is an adeno-associated virus (AAV) vector.

45. A lipid nanoparticle comprising the bidirectional nucleic acid construct of any one of claims 1-17.

46. A host cell comprising the bidirectional nucleic acid construct of any one of claims 1-17.

47. The host cell of claim 46, wherein the host cell is a liver cell.

48. The host cell of any one of claims 46-47, wherein the host cell expresses the AAT polypeptide encoded by the bidirectional construct.

49. Use of the bidirectional nucleic acid construct of any one of claims 1-17 in the manufacture of a medicament for treating AATD, the medicament comprising an endogenous *SERPINA1* gene targeted nucleic acid agent that reduces expression of the endogenous *SERPINA1* gene without significantly reducing expression of the AAT polypeptide coding

sequences of the bidirectional nucleic acid construct, and wherein the medicament is formulated for administration in a subject.

50. The use of claim 49, wherein the endogenous *SERPINA1* gene targeted nucleic acid agent is an siRNA, a dsRNA, or a guide RNA.

51. The use of claim 50, wherein the endogenous *SERPINA1* gene targeted nucleic acid therapeutic agent is selected from an RNAi agent targeted to nucleotides 957-977, 1403-1425, or 1410-1436 of SEQ ID NO: 703, and a guide RNA targeted the endogenous *SERPINA1* gene at a position corresponding to nucleotides 412-431, 506-525, or 538-557 of SEQ ID NO: 703.

52. The use of any one of claims 49-51, wherein the medicament induces a double-stranded break (DSB) within the endogenous *SERPINA1* gene.

53. The use of claim 52, wherein the DSB is induced within the endogenous *SERPINA1* gene at a position corresponding to nucleotides 412-431, 506-525, or 538-557 of SEQ ID NO: 703.

54. The use of any one of claims 49-53, wherein the use comprises modifying the endogenous *SERPINA1* gene.

55. The use of any one of claims 49-54, wherein the *SERPINA1* gene targeted nucleic acid agent is a *SERPINA1* guide RNA that is at least partially complementary to a target sequence present in exon 2, 3, 4, or 5 of the endogenous human *SERPINA1* gene and that targets neither the first AAT polypeptide coding sequence nor the second AAT polypeptide coding sequences.

56. The use of any one of claims 49-55, wherein the *SERPINA1* gene targeted nucleic acid agent is a *SERPINA1* guide RNA that is at least partially complementary to a target sequence within the endogenous *SERPINA1* gene at a position corresponding to nucleotides 412-431, 506-525, or 538-557 of SEQ ID NO: 703.

57. The use of claim 55 or 56, wherein the *SERPINA1* guide RNA comprises:

a guide sequence selected from SEQ ID NOs: 1129-1131;

a guide sequence that is at least 95% identical to SEQ ID NOs: 1129-1131; or

17, 18, 19, or 20 consecutive nucleotides of a sequence chosen from SEQ ID NOs: 1129-1131.

58. The use of any one of claims 49-57, wherein the subject has elevated liver enzymes.

59. The use of claim 58, wherein the subject has at least 3x upper limit of normal (ULN) of one or more liver enzymes.

60. The use of claim 59, wherein the one or more liver enzymes is selected from alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

61. The use of any one of claims 49-60, wherein the medicament reduces elevated liver enzymes to within 3x ULN.

62. The use of any one of claims 49-61, wherein the medicament results in the treatment or prevention of liver fibrosis in the subject.