CLAIMS:

1. A bidirectional nucleic acid construct comprising:

a) a first segment comprising a coding sequence for a first therapeutic polypeptide; and

b) a second segment comprising a reverse complement of a coding sequence for a second therapeutic polypeptide, wherein the first therapeutic polypeptide and the second therapeutic polypeptide are the same therapeutic polypeptide, and

wherein the construct does not comprise any of: (i) a homology arm, (ii) a promoter that drives expression of the coding sequence for the first therapeutic polypeptide, or (iii) a promoter that drives expression of the coding sequence for the second therapeutic polypeptide.

2. The bidirectional nucleic acid construct of claim 1, wherein the 5' end of the second segment is linked to the 3' end of the first segment.

3. The bidirectional nucleic acid construct of claim 1 or 2, wherein the coding sequence for the second therapeutic polypeptide adopts a different codon usage from that of the coding sequence for the first therapeutic polypeptide.

4. The bidirectional nucleic acid construct of any one of claims 1-3, wherein the second segment comprises a nucleotide sequence having at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 97%, or about 99% complementarity to the coding sequence in the first segment.

5. The bidirectional nucleic acid construct of any one of claims 1-4, wherein the second segment comprises a reverse complement of the coding sequence of the first segment, or a fragment thereof.

6. The bidirectional nucleic acid construct of any one of claims 1-5, wherein the first segment is linked to the second segment by a linker.

7. The bidirectional nucleic acid construct of claim 6, wherein the linker is 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 500, 1000, 1500, 2000 nucleotides in length.

8. The bidirectional nucleic acid construct of any one of claims 1-7, wherein each of the first and second segment comprises a polyadenylation sequence, such as a polyadenylation signal sequence or a polyadenylation tail sequence.

9. The bidirectional nucleic acid construct of any of one claims 1-8, wherein the construct comprises a splice acceptor site.

10. The bidirectional nucleic acid construct of claim 9, wherein the construct comprises a first splice acceptor site 5' of the first segment and a second splice acceptor site 3' of the second segment.

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

12. The bidirectional nucleic acid construct of any one of claims 1-10, wherein the construct is double-stranded DNA.

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

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

15. The bidirectional nucleic acid construct of any one of claims 1-14, wherein a sequence encoding the therapeutic polypeptide is codon-optimized.

16. The bidirectional nucleic acid construct of any one of claims 1-15, wherein the construct comprises one or more of the following terminal structures: hairpin, loops, inverted terminal repeats (ITR), or toroid.

17. The bidirectional nucleic acid construct of any one of claims 1-16, wherein the construct comprises one, two, or three inverted terminal repeats (ITR).

18. The bidirectional nucleic acid construct of any one of claims 1-17, wherein the construct comprises no more than two ITRs.

19. The bidirectional nucleic acid construct of any one of claims 1-18, wherein the therapeutic polypeptide is a secreted polypeptide, intracellular polypeptide, variant polypeptide, liver protein, or non-liver protein.

20. The bidirectional nucleic acid construct of any one of claims 1-19, wherein the therapeutic polypeptide, when expressed, comprises a signal peptide.

21. A vector comprising the construct of any one of claims 1-20.

22. The vector of claim 21, wherein the vector is a viral vector.

23. The vector of claim 22, wherein the viral vector is an adeno-associated virus (AAV) vector.

24. A lipid nanoparticle comprising the construct of any one of claims 1-20.

25. A cell or cell population comprising the construct of any one of claims 1-20.

26. The cell or cell population of claim 25, wherein the cell or cell population is a liver cell, a muscle cell, or a neuronal cell, or a population thereof.

27. A composition comprising the construct according to any one of claims 1-20, a vector according to any one of claims 21-23, or the lipid nanoparticle according to claim 24 for use in the treatment of a disease or disorder in a subject, wherein the treatment comprising contacting a cell or cell population in a subject with the construct, vector, or lipid nanoparticle to modify a target locus in the cell or cell population such that the cell or cell population expresses the first therapeutic polypeptide and/or the second therapeutic polypeptide.

28. The composition for use of claim 27, the treatment further comprising providing the cell or cell population with a nuclease, wherein the nuclease is capable of introducing a dsDNA break.

29. The composition for use of claim 27 or 28, the treatment comprising providing the cell or cell population with an RNA-guided DNA-binding agent and a guide RNA (gRNA).

30. The composition for use of claim 29, wherein the gRNA is a single gRNA (sgRNA).

31. The composition for use of claim 29 or 30, wherein the RNA-guided DNA-binding agent is provided as a nucleic acid encoding an RNA-guided DNA-binding agent.

32. The composition for use of claim 29 or 30, wherein the RNA-guided DNA-binding agent is provided as an enzyme or an mRNA encoding an RNA-guided DNA-binding agent.

33. The composition for use of any one of claims 29-32, wherein the RNA-guided DNA-binding agent is a Cas nuclease.

34. The composition for use of claim 33, wherein the Cas nuclease is a class 2 Cas nuclease, or a variant thereof.

35. The composition for use of claim 34, wherein the class 2 Cas nuclease is a Cas9 nuclease.

36. Use of a composition comprising the construct according to any one of claims 1-20, a vector according to any one of claims 21-23, or the lipid nanoparticle according to claim 24, in the manufacture of a medicament for the treatment of a disease or disorder in a subject, wherein the treatment comprising contacting a cell or cell population in a subject with the construct, vector, or lipid nanoparticle to modify a target locus in the cell or cell population such that the cell or cell population expresses the first therapeutic polypeptide and/or the second therapeutic polypeptide.

37. The use of claim 36, the treatment further comprising providing the cell or cell population with a nuclease, wherein the nuclease is capable of introducing a dsDNA break.

38. The use of claim 36 or 37, the treatment comprising providing the cell or cell population with an RNA-guided DNA-binding agent and a guide RNA (gRNA).

39. The use of claim 38, wherein the gRNA is a single gRNA (sgRNA).

40. The use of claim 38 or 39, wherein the RNA-guided DNA-binding agent is provided as a nucleic acid encoding an RNA-guided DNA-binding agent.

41. The use of claim 38 or 39, wherein the RNA-guided DNA-binding agent is provided as an enzyme or an mRNA encoding an RNA-guided DNA-binding agent.

42. The use of any one of claims 38-41, wherein the RNA-guided DNA-binding agent is a Cas nuclease.

43. The use of claim 42, wherein the Cas nuclease is a class 2 Cas nuclease, or a variant thereof.

44. The use of claim 43, wherein the class 2 Cas nuclease is a Cas9 nuclease.

45. A composition comprising the construct according to any one of claims 1-20, the vector according to any one of claims 21-23, or the lipid nanoparticle according to claim 24, for use in therapy.

46. A composition comprising the construct according to any one of claims 1-20, the vector according to any one of claims 21-23, or the lipid nanoparticle according to claim 24, for use in modifying a target locus in a cell or cell population such that the cell or cell population expresses the first therapeutic polypeptide and/or the second therapeutic polypeptide.