We claim:

1. A composition comprising a nucleic acid construct comprising a coding sequence for a multidomain therapeutic protein comprising a CD63-binding delivery domain fused to a lysosomal alpha-glucosidase, wherein the lysosomal alpha-glucosidase coding sequence is CpG-depleted relative to a wild type lysosomal alpha-glucosidase coding sequence.

2. The composition of claim 1, wherein the coding sequence for the multidomain therapeutic protein is at least 99% identical to SEQ ID NO: 196, and

wherein the multidomain therapeutic protein comprises the sequence set forth in SEQ ID NO: 193.

3. The composition of claim 1 or 2, wherein the nucleic acid construct comprises a splice acceptor upstream of the coding sequence for the multidomain therapeutic protein, and the nucleic acid construct comprises a polyadenylation signal or sequence downstream of the coding sequence for the multidomain therapeutic protein.

4. The composition of any one of claims 1-3, wherein the nucleic acid construct does not comprise a homology arm.

5. The composition of any one of claims 1-4, wherein the nucleic acid construct does not comprise a promoter that drives expression of the multidomain therapeutic protein.

6. The composition of any one of claims 1-5, wherein the nucleic acid construct is single-stranded DNA or double-stranded DNA, optionally wherein the nucleic acid construct is single-stranded DNA.

7. The composition of any one of claims 1-6, wherein the nucleic acid construct is in a nucleic acid vector.

8. The composition of claim 7, wherein the nucleic acid vector is an adeno-associated viral (AAV) vector,

optionally wherein the nucleic acid construct is flanked by inverted terminal repeats (ITRs) on each end, optionally wherein the ITR on at least one end comprises, consists

essentially of, or consists of SEQ ID NO: 160, and optionally wherein the ITR on each end comprises, consists essentially of, or consists of SEQ ID NO: 160.

9. The composition of claim 8, wherein the AAV vector is a recombinant AAV8 (rAAV8) vector, optionally wherein the AAV vector is a single-stranded rAAV8 vector.

10. A combination comprising the composition of any one of claims 1-9 and a nuclease agent that targets a nuclease target site in a target genomic locus, wherein the target genomic locus is an *albumin* gene, and wherein the *albumin* gene is a human *albumin* gene, optionally wherein the nuclease target site is in intron 1 of the *albumin* gene.

11. The combination of claim 10, wherein the nuclease agent comprises:

(a) a Cas9 protein or a nucleic acid encoding the Cas9 protein; and

(b) a guide RNA or one or more DNAs encoding the guide RNA, wherein the guide RNA comprises a DNA-targeting segment that targets a guide RNA target sequence, and wherein the guide RNA binds to the Cas9 protein and targets the Cas9 protein to the guide RNA target sequence.

12. The combination of claim 11, wherein:

(I) the DNA-targeting segment comprises SEQ ID NO: 36 or wherein the guide RNA comprises SEQ ID NO: 68 or 100, and wherein the guide RNA comprises at least one modification,

optionally wherein the at least one modification comprises: (i) phosphorothioate bonds between the first four nucleotides at the 5' end of the guide RNA; (ii) phosphorothioate bonds between the last four nucleotides at the 3' end of the guide RNA; (iii) 2'-O-methyl-modified nucleotides at the first three nucleotides at the 5' end of the guide RNA; and (iv) 2'-O-methyl-modified nucleotides at the last three nucleotides at the 3' end of the guide RNA; and

(II) the nucleic acid encoding the Cas9 protein comprises an mRNA encoding the Cas9 protein,

optionally wherein the mRNA encoding the Cas9 protein comprises the sequence set forth in SEQ ID NO: 2, 1, or 12, and the mRNA encoding the Cas9 protein is fully substituted with N1-methyl-pseudouridine, comprises a 5' cap, and comprises a polyadenylation sequence.

13. The combination of claim 11 or 12, wherein the Cas9 protein or the nucleic acid encoding the Cas9 protein and the guide RNA or the one or more DNAs encoding the guide RNA are associated with a lipid nanoparticle,

optionally wherein the lipid nanoparticle comprises a cationic lipid, a neutral lipid, a helper lipid, and a stealth lipid,

optionally wherein the cationic lipid is Lipid A ((9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate),

optionally wherein the cationic lipid is Lipid A, the neutral lipid is DSPC, the helper lipid is cholesterol, and the stealth lipid is PEG2k-DMG, and

optionally wherein the lipid nanoparticle comprises four lipids at the following molar ratios: about 50 mol% Lipid A, about 9 mol% DSPC, about 38 mol% cholesterol, and about 3 mol% PEG2k-DMG.

14. The composition of any one of claims 1-9 or the combination of any one of claims 10-13, for use in inserting the nucleic acid construct encoding the multidomain therapeutic protein into a target genomic locus or expressing the multidomain therapeutic protein from a target genomic locus in a cell or a population of cells in a subject.

15. The composition of any one of claims 1-9 or the combination of any one of claims 10-13, for use in treating a lysosomal alpha-glucosidase deficiency in a subject in need thereof.

16. The composition of any one of claims 1-9 or the combination of any one of claims 10-13, for use in reducing glycogen accumulation in a tissue in a subject in need thereof.

17. The composition of any one of claims 1-9 or the combination of any one of claims 10-13, for use in treating Pompe disease in a subject in need thereof.

18. The composition of any one of claims 1-9 or the combination of any one of claims 10-13, for use in preventing or reducing the onset of a sign or symptom of Pompe disease in a neonatal subject in need thereof.

19. A cell comprising the composition of any one of claims 1-9 or the combination of any one of claims 10-13, optionally wherein:

(I) the nucleic acid construct is integrated into intron 1 of an endogenous *albumin* locus, and multidomain therapeutic protein is expressed from the endogenous *albumin* locus; and/or

(II) the cell is a human cell; and/or

(III) the cell is a liver cell, optionally wherein the liver cell is a hepatocyte; and/or

(IV) the cell is a neonatal cell.

20. The combination for use of any one of claims 14-18, wherein:

(I) the nucleic acid construct is to be administered simultaneously with the nuclease agent; or

(II) the nucleic acid construct is not to be administered simultaneously with the nuclease agent, wherein the nucleic acid construct is to be administered prior to the nuclease agent, or wherein the nucleic acid construct is to be administered after the nuclease agent.