

WHAT IS CLAIMED IS:

1. A polynucleotide encoding a multidomain therapeutic protein comprising a delivery domain and an enzyme domain,
 - wherein the delivery domain binds to an internalization effector;
 - wherein the internalization effector is CD63; and
 - wherein the delivery domain comprises:
 - an amino acid sequence of SEQ ID NO:2, or
 - an amino acid sequence selected from the group consisting of an amino acid sequence of an HCVR set forth in Table 11; an amino acid sequence of a LCVR set forth in Table 11; an amino acid sequence of an HCDR1 set forth in Table 11; an amino acid sequence of an HCDR2 set forth in Table 11; an amino acid sequence of an HCDR3 set forth in Table 11; an amino acid sequence of a LCDR1 set forth in Table 11; an amino acid sequence of a LCDR2 set forth in Table 11; an amino acid sequence of a LCDR3 set forth in Table 11; and an HCVR/LCVR amino acid pair set forth as SEQ ID NOs:14/22, SEQ ID NOs:30/38, SEQ ID NOs:46/54, or SEQ ID NOs:62/70, wherein the HCVR/LCVR amino acid pair comprises from N-terminal to C-terminal: the HCVR, an optional linker, and the LCVR.
2. The polynucleotide of claim 1, wherein the enzyme domain comprises a hydrolase.
3. The polynucleotide of claim 1, wherein the enzyme domain comprises a glycosylase.
4. The polynucleotide of claim 1, wherein the enzyme domain comprises a glycosidase.
5. The polynucleotide of claim 1, wherein the enzyme domain comprises an alpha-glucosidase.
6. The polynucleotide of claim 1, wherein the enzyme domain comprises an amino acid sequence of SEQ ID NO:1.

7. The polynucleotide of claim 1, further comprising a virus nucleic acid sequence and/or a locus-targeting nucleic acid sequence.

8. The polynucleotide of claim 1, further comprising a virus nucleic acid sequence and at least one of (i) a locus-targeting nucleic acid sequence, (ii) a tissue specific regulatory element, or (iii) a combination of (i) and (ii);

wherein the virus nucleic acid sequence is an adeno-associated virus (AAV) nucleic acid internal terminal repeat sequence comprising a sequence set forth as SEQ ID NO:6, SEQ ID NO:7, or a combination thereof,

wherein the locus-targeting nucleic acid sequence targets the polynucleotide to a locus selected from the group consisting of an EESYR locus, a SARS locus, position 188,083,272 of human chromosome 1 or its non-human mammalian orthologue, position 3,046,320 of human chromosome 10 or its non-human mammalian orthologue, position 67,328,980 of human chromosome 17 or its non-human mammalian orthologue, an adeno-associated virus site 1 (AAVS1) on human chromosome 19 or its non-human mammalian orthologue, a chemokine receptor 5 (CCR5) gene, a chemokine receptor gene encoding an HIV-1 coreceptor, a mouse Rosa26 locus or its non-murine mammalian orthologue, and a human albumin (*alb*) locus, and

wherein the tissue specific regulatory element is a liver specific enhancer comprising the sequence set forth as SEQ ID NO:9 and/or a liver specific promoter comprising the sequence set forth as SEQ ID NO:8.

9. A polynucleotide encoding a multidomain therapeutic protein comprising a delivery domain and an enzyme domain, wherein the delivery domain binds to an internalization effector, and wherein the polynucleotide comprises a nucleic acid sequence of SEQ ID NO:11 and/or encodes an amino acid sequence set forth as SEQ ID NO:10 or SEQ ID NO:79.

10. A composition comprising a gene therapy vector comprising the polynucleotide of claim 1,

wherein the gene therapy vector is selected from the group consisting of (i) a viral vector comprising the polynucleotide, (ii) the polynucleotide by itself as a naked polynucleotide,

(iii) a complex comprising the polynucleotide complexed with a metal, a cation, an anion, a lipid, a polymer, and any combination thereof, and (iv) any combination of (i)-(iii).

11. The composition of claim 10, wherein the gene therapy vector is a viral vector selected from the group consisting of a retrovirus, adenovirus, herpes simplex virus, pox virus, vaccinia virus, lentivirus, or an adeno-associated virus.

12. The composition of claim 11, wherein the gene therapy vector is an AAV2/8 chimera.

13. The composition of claim 10, further comprising a pharmaceutically acceptable carrier, wherein the composition is a pharmaceutically acceptable composition for administration into a subject, and

wherein the composition comprises a therapeutically effective amount of the polynucleotide.

14. A recombinant multidomain therapeutic protein comprising a delivery domain and an enzyme domain, wherein the protein is encoded by the polynucleotide according to claim 1.

15. The recombinant multidomain therapeutic protein of claim 14, comprising a sequence set forth as SEQ ID NO:10 or SEQ ID NO:79.

16. A method of expressing in a cell *in vitro* a recombinant multidomain therapeutic protein comprising a delivery domain and an enzyme domain, the method comprising:

- a. contacting the cell with the composition of claim 10;
- b. allowing the polynucleotide to integrate into a genomic locus of the cell;

and

c. allowing the cell to produce the recombinant multidomain therapeutic protein.

17. The method of claim 16, wherein the genomic locus of the cell is a safe harbor locus selected from the group consisting of an EESYR locus, a SARS locus, position 188,083,272 of

human chromosome 1 or its non-human mammalian orthologue, position 3,046,320 of human chromosome 10 or its non-human mammalian orthologue, position 67,328,980 of human chromosome 17 or its non-human mammalian orthologue, an adeno-associated virus site 1 (AAVS1) on human chromosome 19 or its non-human mammalian orthologue, a chemokine receptor 5 (CCR5) gene, a chemokine receptor gene encoding an HIV-1 coreceptor, a mouse Rosa26 locus or its non-murine mammalian orthologue, and a human albumin (*alb*) locus.

18. The method of claim 16, wherein the polynucleotide comprises a nucleic acid sequence of SEQ ID NO:11 and/or encodes an amino acid sequence set forth as SEQ ID NO:10 or SEQ ID NO:79.

19. The polynucleotide of claim 1, wherein the enzyme domain comprises an amino acid sequence of SEQ ID NO:13.

20. The polynucleotide of claim 1, wherein the enzyme domain comprises an amino acid sequence of SEQ ID NO:78.