CLAIMS:

1. A closed-ended DNA (ceDNA) system comprising a first inverted terminal repeat (ITR), a second ITR, and a genetic cassette;

wherein the first ITR and the second ITR is an ITR from a non-adeno-associated virus (non-AAV),

wherein the non-AAV ITR comprises a nucleotide sequence at least 80% identical to SEQ ID NO: 167, 168, 169, 170, 171, 172, 173, 174, 175, or 176,

wherein the non-AAV ITR retains a functional property of an erythrovirus parvovirus B19 or a goose parvovirus (GPV) strain,

wherein the genetic cassette is positioned between the first ITR and the second ITR,

wherein the genetic cassette encodes a therapeutic protein, or a miRNA, and

wherein the system is capsid-free.

2. The system of claim 1, wherein the therapeutic protein comprises a clotting factor.

3. The system of claim 1, wherein the ITR comprises a nucleotide sequence at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO: 167, 168, 169, 170 or 171, wherein the ITR retains the functional property of an ITR of the erythrovirus parvovirus B19.

4. The system of claim 1, wherein the ITR comprises a nucleotide sequence at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID NO: 172, 173, 174, 175 or 176, wherein the ITR retains the functional property of an ITR of the goose parvovirus (GPV) strain.

5. The system of any one of claims 1 to 4, where the first and/or second ITR is a truncated ITR which comprises or consists of a fragment of a naturally occurring ITR, and retains a functional property of the naturally occurring ITR.

6. The system of any one of claims 1 to 5, which further comprises a promoter.

7. The system of claim 6, wherein the promoter drives expression of the therapeutic protein in hepatocytes, endothelial cells, muscle cells, sinusoidal cells, or any combination thereof.

8. The system of claim 6, wherein the promoter is selected from the group consisting of a mouse thyretin promoter (mTTR), an endogenous human factor VIII promoter (F8), a human alpha-1-antitrypsin promoter (hAAT), a human albumin minimal promoter, a mouse albumin promoter, a tristetraprolin (TTP) promoter, a CASI promoter, a CAG promoter, a cytomegalovirus (CMV) promoter, α1-antitrypsin (AAT), muscle creatine kinase (MCK), myosin heavy chain alpha (αMHC), myoglobin (MB), desmin (DES), SPc5-12, 2R5Sc5-12, dMCK, tMCK, and a phosphoglycerate kinase (PGK) promoter.

9. The system of any one of claims 2 to 8, wherein the genetic cassette further comprises:
(a) an intronic sequence,
(b) a post-transcriptional regulatory element,
(c) a 3'UTR poly(A) tail sequence,
(d) an enhancer sequence, or
(e) any combination of (a) – (d).

10. The system of claim 9, wherein:

(a) the intronic sequence is positioned 5' to a nucleic acid sequence encoding the clotting factor;
(b) the post-transcriptional regulatory element comprises a mutated woodchuck hepatitis virus post-transcriptional regulatory element (WPRE), a microRNA binding site, a DNA nuclear targeting sequence, or any combination thereof;
(c) the 3'UTR poly(A) tail sequence is selected from the group consisting of bGH poly(A), actin poly(A), hemoglobin poly(A), and any combination thereof; or
(d) any combination of (a) – (c).

11. The system of claim 10, wherein:

(a) the intronic sequence comprises SEQ ID NO: 115;
(b) the post-transcriptional regulatory element comprises a microRNA binding site to miR142-3p;
(c) the 3'UTR poly(A) tail sequence comprises bGH poly(A); or
(d) any combination of (a) – (c).

12. The system of any one of claims 2 to 11, wherein the system comprises in this order:

(a) the first ITR, which is an ITR of erythrovirus parvovirus B19 or Goose parvovirus (GPV);

(b) a TTP promoter;

(c) a synthetic intron;

(d) a nucleotide sequence, which encodes a clotting factor;

(e) a post-transcriptional regulatory element, which comprises WPRE;

(f) a 3'UTR poly(A) tail sequence, which comprises bGHpA; and

(g) the second ITR, which is an ITR of erythrovirus parvovirus B19 or Goose parvovirus (GPV).

13. The system of any one of claims 2 to 12, wherein the clotting factor comprises factor I (FI), factor II (FII), factor V (FV), factor VII (FVII), factor VIII (FVIII), factor IX (FIX), factor X (FX), factor XI (FXI), factor XII (FXII), factor XIII (FVIII), Von Willebrand factor (VWF), prekallikrein, high-molecular weight kininogen, fibronectin, antithrombin III, heparin cofactor II, protein C, protein S, protein Z, Protein Z-related protease inhibitor (ZPI), plasminogen, alpha 2-antiplasmin, tissue plasminogen activator(tPA), urokinase, plasminogen activator inhibitor-1 (PAI-1), plasminogen activator inhibitor-2 (PAI2), or any combination thereof.

14. The system of claim 13, wherein the FVIII comprises an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to an amino acid sequence as set forth in a sequence selected from SEQ ID NOs: 103, 106, and 109.

15. The system of claim 13, wherein the nucleic acid encoding the FVIII comprises a nucleotide sequence of at least 60% at least 65%, at least 70% at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to a nucleotide sequence of SEQ ID NO: 107.

16. The system of any one of claims 2 to 15, wherein the clotting factor comprises a heterologous moiety selected from the group consisting of albumin or a fragment thereof, an immunoglobulin Fc region, the C-terminal peptide (CTP) of the β subunit of human chorionic gonadotropin, a PAS sequence, a HAP sequence, a transferrin or a fragment thereof, an albumin-binding moiety, a derivative thereof, or any combination thereof.

17. The system of any one of claims 13 to 16, wherein the clotting factor comprises a FVIII and further comprises an FcRn binding partner.

18. The system of any one of claims 1 to 17, wherein the nucleic acid molecule is formulated with a delivery agent comprising a lipid nanoparticle.

19. The system of any one of claims 1 to 18, wherein the nucleic acid molecule is a single stranded nucleic acid.

20. A pharmaceutical composition comprising the system of any one of claims 1 to 19 and a pharmaceutically acceptable carrier.

21. The system of any one of claims 2 to 19 or the pharmaceutical composition of claim 20, for use for expressing a clotting factor in a subject in need thereof.