CLAIMS:

1. A ~~nucleic acid molecule~~system comprising a first inverted terminal repeat (ITR), a second ITR, and a genetic cassette;

wherein the first ITR and/or the second ITR ~~are~~is an ITR ~~off~~from a non-adeno-associated virus (non-AAV),

~~wherein the non-AAV ITR is derived from an ITR of a member of the viral family *Parvoviridae* selected from the group consisting of *Bocavirus*, *Dependovirus*, *Erythrovirus*, *Amdovirus*, *Densovirus*, *Iteravirus*, *Contravirus*, *Aveparvovirus*, *Copiparvovirus*, *Protoparvovirus*, *Tetraparvovirus*, *Ambidensovirus*, *Brevidensovirus*, *Hepandensovirus*, *Penstyldensovirus*, Muscovy duck parvovirus (MDPV) strain, porcine parvovirus (U44978), mice minute virus (U34256), canine parvovirus (M19296), and mink enteritis virus (D00765),~~

~~wherein the nucleotide sequence of the non-AAV ITR is at least 50% identical to the nucleotide sequence of the ITR from the member of the viral family *Parvoviridae* and retains a functional property of the ITR from the member of the viral family *Parvoviridae*,~~

wherein the non-AAV ITR is derived from an ITR of erythrovirus parvovirus B19 and Goose parvovirus (GPV),

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

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

wherein the system is capsid-free.

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

3. The ~~nucleic acid molecule~~system of claim 1 ~~or 2, wherein the member of the viral family *Parvoviridae* is *Dependovirus* or *Erythrovirus*.~~

~~4. The nucleic acid molecule of any one of claims 1 to 3, wherein the first ITR and the second ITR are ITRs of a non-AAV.~~

~~5. The nucleic acid molecule of any one of claims 1 to 3, wherein the first ITR is an ITR of a non-AAV and the second ITR is an ITR of an adeno-associated virus (AAV) or wherein the first ITR is an ITR of an AAV and the second ITR is an ITR of a non-AAV.~~

~~6. The nucleic acid molecule of any one of claims 1 to 5, wherein the member of the viral family *Parvoviridae* is erythrovirus parvovirus B19 (human virus).~~

~~7. The nucleic acid molecule of claim 6~~, wherein the ITR comprises the sequence of SEQ ID NO: 167, 168, 169, 170 or 171.

~~8. The nucleic acid molecule of any one of claims 1 to 5, wherein the viral family *Parvoviridae* is a *Dependovirus* Goose parvovirus (GPV) strain.~~

~~9. The nucleic acid molecule of claim 8~~

4. The system of claim 1, wherein the ITR comprises the sequence of SEQ ID NO: 172, 173, 174, 175 or 176.

~~10~~

5. The ~~nucleic acid molecule~~system of any one of claims 1 to ~~9~~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.

~~11~~

6. The ~~nucleic acid molecule of any one of claim 1 to 10, wherein the first ITR and the second ITR are derived from the genomes of two different virus genomes.~~

~~12. The nucleic acid molecule~~system of any one of claims 1 to ~~11~~5, which further comprises a promoter.

~~13~~

7. The ~~nucleic acid molecule~~system of claim ~~10~~5, wherein the promoter drives expression of the therapeutic protein in hepatocytes, endothelial cells, muscle cells, sinusoidal cells, or any combination thereof.

~~14~~

8. The ~~nucleic acid molecule~~system of claim ~~10 or 11~~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.

~~15~~

9. The ~~nucleic acid molecule~~system of any one of claims 2 to ~~14~~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).

~~16~~

10. The nucleic acid molecule of claim ~~15~~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).

~~17~~

11. The nucleic acid molecule of claim ~~16~~10, wherein:

(a) the intronic sequence comprises SEQ ID NO: 115;

(b) the post-transcriptional regulatory element comprises a microRNA binding site ~~comprises a binding site~~ to miR142-3p;

(c) the 3'UTR poly(A) tail sequence comprises bGH poly(A); or

(d) any combination of (a) – (c).

~~18~~

12. The nucleic acid molecule of any one of claims 2 to ~~17~~11, wherein the nucleic acid molecule comprises in this order:

(a) the first ITR, which is an ITR of ~~a non-AAV family member of *Parvoviridae*~~

~~selected from the group consisting of *Bocavirus*, *Dependovirus*, *Erythrovirus*, *Amdovirus*, *Densovirus*, *Iteravirus*, *Contravirus*, *Aveparvovirus*, *Copiparvovirus*, *Protoparvovirus*, *Tetraparvovirus*, *Ambidensovirus*, *Brevidensovirus*, *Hepandensovirus*, *Penstyldensovirus*, Muscovy duck~~erythrovirus parvovirus ~~(MDPV) strain, porcine~~B19 or Goose parvovirus (~~U44978), mice minute virus (U34256), canine parvovirus (M19296), and mink enteritis virus (D00765~~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 ~~a non-AAV family member of *Parvoviridae*~~

~~selected from the group consisting of *Bocavirus*, *Dependovirus*, *Erythrovirus*, *Amdovirus*, *Densovirus*, *Iteravirus*, *Contravirus*, *Aveparvovirus*, *Copiparvovirus*, *Protoparvovirus*, *Tetraparvovirus*, *Ambidensovirus*, *Brevidensovirus*, *Hepandensovirus*, *Penstyldensovirus*,~~

~~Muscovy duck~~erythrovirus parvovirus ~~(MDPV) strain, porcine~~B19 or Goose parvovirus (~~U44978), mice minute virus (U34256), canine parvovirus (M19296), and mink enteritis virus (D00765~~GPV).

~~19~~

13. The ~~nucleic acid molecule~~system of any one of claims 2 to ~~18~~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.

~~20~~

14. The ~~nucleic acid molecule~~system of claim ~~19~~13, wherein the FVIII comprises an amino acid sequence at least ~~about~~ 70%, at least ~~about~~ 75%, at least ~~about~~ 80%, at least ~~about~~ 85%, at least ~~about~~ 90%, at least ~~about~~ 95%, at least ~~about~~ 96%, at least ~~about~~ 97%, at least ~~about~~ 98%, at least ~~about~~ 99%, or 100% identical to an amino acid sequence as set forth in a sequence selected from SEQ ID NOs: 103, 106, and 109.

~~21~~

15. The ~~nucleic acid molecule~~system of claim ~~19~~13, wherein the nucleic acid encoding the FVIII comprises a nucleotide sequence of at least ~~about~~ 60% at least ~~about~~ 65%, at least ~~about~~ 70% at least ~~about~~ 75%, at least ~~about~~ 80%, at least ~~about~~ 85%, at least ~~about~~ 90%, at least ~~about~~ 95%, at least ~~about~~ 96%, at least ~~about~~ 97%, at least ~~about~~ 98%, at least ~~about~~ 99%, or ~~about~~ 100% identical to a nucleotide sequence of SEQ ID NO: 107.

~~22~~

16. The ~~nucleic acid molecule~~system of any one of claims 2 to ~~21~~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.

~~23~~

17. The ~~nucleic acid molecule~~system of any one of claims ~~19~~13 to ~~22~~16, wherein the clotting factor comprises a FVIII and further comprises an FcRn binding partner.

~~24~~

18. The ~~nucleic acid molecule~~system of any one of claims 1 to ~~23~~17, wherein the nucleic acid molecule is formulated with a delivery agent comprising a lipid nanoparticle.

~~25~~

19. The ~~nucleic acid molecule~~ system of any one of claims 1 to ~~24~~18, wherein the nucleic acid molecule is a single stranded nucleic acid.

~~26. The nucleic acid molecule of any one of claims 1 to 24, which is in the form of a closed-end DNA (ceDNA).~~

~~27~~

20. A pharmaceutical composition comprising the ~~nucleic acid molecule~~system of any one of claims 1 to ~~26~~19 and a pharmaceutically acceptable carrier.

~~28~~

21. The nucleic acid molecule of any one of claims 2 to ~~26~~19 or the pharmaceutical composition of claim ~~27~~20, for use for expressing a clotting factor in a subject in need thereof.

~~29. A baculovirus system for production of the nucleic acid molecule of any one of claims 1-26 wherein the nucleic acid molecule is produced in insect cells.~~