CLAIMS

1. A non-viral capsid- free DNA vector with covalently-closed ends (ceDNA vector), wherein the ceDNA vector comprises at least one heterologous nucleotide sequence operably positioned between two flanking symmetric inverted terminal repeats (symmetric ITRs), wherein the symmetric ITRs are not wild-type ITRs, and wherein each of the flanking symmetric ITRs is modified by a deletion, an insertion, and/or a substitution in the A' and/or A region, wherein the one of the flanking symmetric ITRs comprises a sequence having at least 95% identity to SEQ ID NO:497 (ITR-46 left), wherein the other flanking symmetric ITR comprises a sequence having 95% identity to SEQ ID NO: 481 (ITR-30, right), and wherein each flanking ITR has the same symmetrical modification.

2. The ceDNA vector of claim 1, wherein the two flanking symmetric ITRs comprise a pair of ITRs consisting of SEQ ID NO:497 (ITR-46 left) and SEQ ID NO: 481 (ITR-30, right).

3. The ceDNA vector of claim 1, wherein the flanking symmetric ITRs are synthetic.

4. The ceDNA vector of any one of claims 1-3, wherein the ceDNA vector comprises an aptamer.

5. The ceDNA vector of any one of claims 1-4, wherein the ceDNA vector comprises at least one regulatory switch.

6. The ceDNA vector of any one of claims 1-5, wherein the symmetric ITRs are derived from a virus selected from the group consisting of a parvovirus, a dependovirus, and an adeno-associated virus (AAV).

7. The ceDNA vector of claim 6, wherein the symmetric ITRs are derived from an AAV serotype selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, and AAV12.

8. The ceDNA vector of any one of claims 1-7, wherein the vector is in a lipid nanoparticle (LNP).

9. The ceDNA vector of any one of claims 1-8, the ceDNA vector being obtained from a process comprising the steps of:

(a) incubating a population of insect cells harboring a ceDNA expression construct in the presence of at least one Rep protein, wherein the ceDNA expression construct encodes the ceDNA

vector, under conditions effective and for a time sufficient to induce production of the ceDNA vector within the insect cells; and

(b) isolating the ceDNA vector from the insect cells.

10. The ceDNA vector of claim 9, wherein the insect cells express at least one Rep protein.

11. A ceDNA expression construct that encodes the ceDNA vector of any one of claims 1-10.

12. A host cell comprising the ceDNA expression construct of claim 11.

13. The host cell of claim 12, which expresses at least one Rep protein.

14. The host cell of claim 13, wherein the at least one Rep protein is derived from a virus selected from the group consisting of: a parvovirus, a dependovirus, and an adeno-associated virus (AAV).

15. The host cell of claim 14, wherein the at least one Rep protein is derived from an AAV serotype selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, and AAV12.

16. The host cell of any one of claims 12-15, wherein the host cell is an insect cell.

17. The host cell of claim 16, wherein the insect cell is an Sf9 cell.

18. A method of producing a ceDNA vector, comprising: (a) incubating the host cell of any one of claims 12-17 under conditions effective and for time sufficient to induce production of the ceDNA vector; and (b) isolating the ceDNA from the host cell.

19. Use of the ceDNA vector of any one of claims 1-10 in the manufacture of a medicament for treating, preventing, ameliorating, monitoring, or diagnosing a disease or disorder in a subject.

20. The use of claim 19, wherein the at least one heterologous nucleic acid sequence, when transcribed or translated, modifies an abnormal amount, function or activity of an endogenous protein in the subject.

21. The use of claim 19, wherein the at least one heterologous nucleic acid sequence encodes or comprises a nucleotide molecule selected from the group consisting of an RNAi, an siRNA, an miRNA, an IncRNA, an aptamer and an antisense oligo- or polynucleotide;

wherein the at least one heterologous nucleic acid sequence encodes a protein;

wherein the at least one heterologous nucleic acid sequence encodes an agonist or an antagonist of an endogenous protein or pathway associated with the disease or disorder; or

wherein the at least one-heterologous nucleic acid sequence encodes an antibody.

22. The use of any one of claims 19 to 21, wherein the disease or disorder is selected from the group consisting of:

a metabolic disease or disorder, wherein the metabolic disease or disorder is selected from the group consisting of diabetes, a lysosomal storage disorder, a mucopolysaccharide disorder, a urea cycle disease or disorder, and a glycogen storage disease or disorder; wherein the lysosomal storage disorder is selected from the group consisting of Gaucher's disease, Pompe disease, metachromatic leukodystrophy (MLD), phenylketonuria (PKU), and Fabry disease; wherein the urea cycle disease or disorder is ornithine transcarbamylase (OTC) deficiency; wherein the mucopolysaccharide disorder is selected from the group consisting of Sly syndrome, Hurler Syndrome, Scheie Syndrome, Hurler-Scheie Syndrome, Hunter's Syndrome, Sanfilippo Syndrome, Morquio Syndrome, and Maroteaux-Lamy Syndrome;

a CNS disease or disorder, wherein the CNS disease or disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Canavan disease, Leigh's disease, Refsum disease, Tourette syndrome, primary lateral sclerosis, amyotrophic lateral sclerosis, progressive muscular atrophy, Pick's disease, muscular dystrophy, multiple sclerosis, myasthenia gravis, Binswanger's disease, trauma due to spinal cord or head injury, Tay Sachs disease, Lesch-Nyan disease, epilepsy, cerebral infarcts, psychiatric disorders, schizophrenia, drug dependency, neuroses, psychosis, dementia, paranoia, attention deficit disorder, sleep disorders, pain disorders, eating or weight disorders, and cancers and tumors of the CNS;

an ocular disease or disorder, wherein the ocular disease or disorder is selected from the group consisting of an ophthalmic disorder involving the retina, posterior tract, and/or optic nerve; wherein the ophthalmic disorder involving the retina, posterior tract, and/or optic nerve are selected from the group consisting of diabetic retinopathy, macular degeneration including age-related macular degeneration, geographic atrophy and vascular or "wet" macular degeneration, glaucoma, uveitis, retinitis pigmentosa, Stargardt, Leber Congenital Amaurosis (LCA), Usher syndrome, pseudoxanthoma elasticum (PXE), x-linked retinitis pigmentosa (XLRP), x-linked retinoschisis (XLRS), Choroideremia, Leber hereditary optic neuropathy (LHON), Archomatopsia, cone-rod dystrophy, Fuchs endothelial corneal dystrophy, diabetic macular edema and ocular cancer and tumors;

a blood disease or disorder, wherein the blood disease or disorder is selected from the group consisting of hemophilia A, hemophilia B, thalassemia, anemia, and blood cancers;

a liver disease or disorder, wherein the liver disease or disorder is selected from the group consisting of progressive familial intrahepatic cholestasis (PFIC) and liver cancer, and tumors;

cystic fibrosis; and

an immune disease or disorder, an infectious disease, a muscular disease or disorder, cancer, and a disease or disorder based on an abnormal level and/or function of a gene product.

23. The use of any one of claims 19 to 22, wherein the ceDNA vector further comprises an aptamer.

24. Use of the ceDNA vector of any one of claims 1-10 in the manufacture of a medicament for delivering a therapeutic protein to a subject, wherein the at least one heterologous nucleic acid sequence encodes a therapeutic protein.

25. A kit comprising a ceDNA vector of any of claims 1-10, and a nanocarrier, packaged in a container with instructions for use.

26. The ceDNA vector of any one of claims 1-10 for use in therapy.