examples in which satisfactory therapeutic effect is obtained. Thus, there is a need for alternative methods of delivering nucleic acid molecules to subjects for gene therapy applications.

SUMMARY

In one aspect, the present invention refers to the use of a composition in the manufacture of a medicament for gene therapy of a disease or condition, wherein: the composition comprises a delivery agent comprising a therapeutic nucleic acid molecule, and an agent that facilitates entry of the delivery agent into the parenchymal cells in a compartmentalized tissue or organ or portion of a tissue or organ; the organ or tissue or portion thereof is the liver or a portion of the liver; the delivery agent is a virus that comprises the therapeutic nucleic acid molecule; the agent that facilitates entry into the parenchymal cells comprises a transcriptional enhancer of a virus-specific cell surface receptor; the composition contains a single dose that is therapeutically effective for administration without dilution into the parenchyma of the liver or portion thereof that is to be compartmentalized for at least 25 minutes up to 1 hour following administration for quantitative uptake of the administered virus or viral vector; a single dosage of the composition contains $1x10^3$ to $1x10^{12}$ viral particles; the nucleic acid molecule encodes an enzyme, a hormone, a coagulation or clotting factor, a cytokine, a growth factor or active portion thereof, an antibody or antigen binding portion thereof, an angiogenesis modulator, an immunomodulator, a pain modulator, a receptor or active portion thereof, a transport protein or a regulatory protein, for treating a disease or condition; the disease or condition is selected from among arthritis, chronic pain, HIV-related AIDS, atherosclerosis, restenosis, inherited enzyme deficiency, inherited immune deficiency, cancer, a retrovirus infection, hemophilia, diabetes, a muscular dystrophy, a dystrophy, a cardiovascular disorder, cystic fibrosis, a neurodegenerative disorder, trauma, pain, sickle cell anemia, autoimmune disease, inflammatory disease and hypertension; the composition is to be administered into the parenchyma of a compartmentalized tissue, organ, or portion of a tissue or organ sufficient in size to compartmentalize and for administration of the composition; the parenchyma in the compartmentalized tissue or organ or portion thereof does not include connective tissue, blood vessels, nerves or ducts; and a compartmentalized tissue or organ or portion of a tissue or organ is a tissue or organ that has been clamped to isolate it from the systemic circulation, whereby the arteries, veins, ducts and/or vessels servicing or traversing the tissue or organ or portion of the tissue or organ are blocked so that blood supply and flow to the tissue or organ or portion thereof is reduced or eliminated.

In one example, there is disclosed the use of a composition in the manufacture of a medicament for gene therapy of a disease or condition, wherein: the

composition comprises: a delivery agent comprising a therapeutic nucleic acid molecule and an agent that facilitates entry of the delivery agent into the parenchymal cells in a compartmentalized tissue or organ or portion of a tissue or organ; and molecule; the organ or tissue or portion thereof is the liver or a portion of the liver; the delivery agent is a virus that comprises the therapeutic nucleic acid; the agent that facilitates entry comprises a transcriptional enhancer of a virus-specific cell surface receptor; the composition contains a single dose that is therapeutically effective for administration without dilution into the parenchyma of the liver or portion thereof that is to be compartmentalized for at least 25 minutes up to 1 hour following administration for quantitative uptake of the administered virus or viral vector; a single dosage of the composition contains 1 x 10^3 to 1 x 10^{12} viral particles; the nucleic acid molecule encodes an enzyme, a hormone, a coagulation or clotting factor, a cytokine, a growth factor or active portion thereof, an antibody or antigen binding portion thereof, an angiogenesis modulator, an immunomodulator, a pain modulator, a receptor or active portion thereof, a transport protein or a regulatory protein for treating a disease or condition; the disease or condition is selected from among arthritis, chronic pain, HIV-related AIDS, atherosclerosis, restenosis, inherited enzyme deficiency, inherited immune deficiency, cancer, a retrovirus infection, hemophilia, a muscular dystrophy, a dystrophy, a cardiovascular disorder, cystic fibrosis, a neurodegenerative disorder, trauma, pain, sickle cell anemia, autoimmune disease, inflammatory disease and hypertension; the composition is formulated for administration into the parenchyma of a compartmentalized tissue, organ, or portion of a tissue or organ sufficient in size to compartmentalize and for administration of the composition; the parenchyma in the compartmentalized tissue or organ or portion thereof does not include connective tissue, blood vessels, nerves or ducts; and a compartmentalized tissue or organ or portion of a tissue or organ is a tissue or organ that has been clamped to isolate it from the systemic circulation, whereby the arteries, veins, ducts and/or vessels servicing or traversing the tissue or organ or portion of the tissue or organ are blocked so that blood supply and flow to the tissue or organ or portion thereof is reduced or eliminated.

In another aspect, the present invention refers to a composition for direct delivery of a therapeutic nucleic acid molecule into parenchyma cells of an organ or tissue for treatment of a disease or condition, comprising: a delivery agent comprising a nucleic acid molecule that encodes an enzyme, a hormone, a coagulation or clotting factor, a cytokine, a growth factor or active portion thereof, an antibody or antigen binding portion thereof, an angiogenesis modulator, an immunomodulator, a pain modulator, a receptor or active portion thereof, a transport protein or a regulatory protein, for treating a disease or condition; and an agent that facilitates entry of the delivery agent into the parenchymal cells in a compartmentalized tissue or organ or portion of a tissue or organ, wherein: the delivery agent is a virus; the composition

comprises a transcriptional enhancer of a virus-specific cell surface receptor; a therapeutically effective single dosage of the composition contains $1x10^3$ to $1x10^{12}$ viral particles; the composition is formulated for direct administration of the delivery agent comprising the nucleic acid molecule into the parenchyma of a compartmentalized tissue, organ, or portion of a tissue or organ sufficient in size to compartmentalize and for administration of the composition; a compartmentalized tissue or organ or portion of a tissue or organ is a tissue or organ that has been isolated from the systemic circulation, whereby the arteries, veins, ducts and/or vessels servicing or traversing the tissue or organ or portion of the tissue or organ are blocked so that blood supply and flow to the tissue or organ or portion thereof is reduced or eliminated; and the disease or condition is selected from among arthritis, chronic pain, HIV-related AIDS, atherosclerosis, restenosis, inherited enzyme deficiency, inherited immune deficiency, cancer, a retrovirus infection, hemophilia, diabetes, a muscular dystrophy, a dystrophy, a cardiovascular disorder, cystic fibrosis, a neurodegenerative disorder, trauma, pain, sickle cell anemia, autoimmune disease, inflammatory disease and hypertension. In one example, there is described a composition for direct delivery of a therapeutic nucleic acid molecule into parenchyma cells of an organ or tissue for treatment of a disease or condition, comprising: a delivery agent comprising a nucleic acid molecule that encodes an enzyme, a hormone, a coagulation or clotting factor, a cytokine, a growth factor or active portion thereof, an antibody or antigen binding portion thereof, an angiogenesis modulator, an immunomodulator, a pain modulator, a receptor or active portion thereof, a transport protein or a regulatory protein for treating a disease or condition; and an agent that facilitates entry of the delivery agent into the parenchymal cells in a compartmentalized tissue or organ or portion of a tissue or organ, wherein: the delivery agent is a virus; the composition comprises a transcriptional enhancer of a virus-specific cell surface receptor; a therapeutically effective single dosage of the composition contains $1x10^3$ to 1×10^{12} viral particles; the composition is formulated for direct administration of the delivery agent comprising the nucleic acid molecule into the parenchyma of a compartmentalized tissue, organ, or portion of a tissue or organ sufficient in size to compartmentalize and for administration of the composition; a compartmentalized tissue or organ or portion of a tissue or organ is a tissue or organ that has been isolated from the systemic circulation, whereby the arteries, veins, ducts and/or vessels servicing or traversing the tissue or organ or portion of the tissue or organ are blocked so that blood supply and flow to the tissue or organ or portion thereof is reduced or eliminated; and the disease or condition is selected from among arthritis, chronic pain, HIV-related AIDS, atherosclerosis, restenosis, inherited enzyme deficiency, inherited immune deficiency, cancer, a retrovirus infection, hemophilia, a muscular dystrophy, a dystrophy, a cardiovascular

disorder, cystic fibrosis, a neurodegenerative disorder, trauma, pain, sickle cell anemia, autoimmune disease, inflammatory disease and hypertension.

In another embodiment, there is provided a composition, comprising an adenovirus or adeno-associated virus comprising heterologous nucleic acid in its genome, wherein:

the composition is formulated for single dosage administration for gene therapy and contains less than 1×10^7 viral particles ; and

the composition comprises a transcriptional enhancer of a virus-specific cell surface receptor.

Provided herein is a method of delivering a nucleic acid molecule to a subject. The method can be used in gene therapy applications, including in applications to treat diseases and conditions as well as in industrial, agricultural and veterinary applications. As provided herein, the method includes a) compartmentalizing a tissue or organ or portion of the tissue or organ from systemic circulation of the host; and b) administering a delivered agent directly to the parenchyma of the tissue or organ or portion of the tissue or organ, wherein the delivered agent contains the nucleic acid molecule, whereby the delivered agent enters parenchymal cells of the compartmentalized tissue or organ or portion of the tissue or organ. Compartmentalizing the tissue or organ or portion of the tissue or organ can be effected prior to, simultaneous or subsequent to administering the delivered agent. Generally, compartmentalization of the tissue or organ or portion of the tissue or organ is initiated prior to administering the delivered agent, and typically no more than 5 minutes, 4 minutes, 3 minutes, 2 minutes, 1 minute or 30 seconds before delivery of the delivered agent containing a nucleic acid molecule.

The method provided can further include a step of restoring communication between the tissue, organ or portion of the tissue or organ with the systemic circulation. The step of restoring communication is generally a predetermined time after administering the delivered agent. The predetermined time is a time period that is sufficient for the administered delivered agent to enter parenchymal cells (*e.g.* by transduction), whereby upon restoration of communication no more than 20% of the delivered agent has not entered a parenchymal cell. For example, no more than 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, or 5% of the delivered agent has not entered a parenchymal cell. In some examples, the predetermined times is a time period sufficient for the administered delivered agent to enter parenchymal cells, whereby upon restoration of communication no more than 20% of the delivered agent is exposed to the systemic circulation. For example, no more than 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, or 5% of the delivered agent is exposed to the

Claims:

1. Use of a composition in the manufacture of a medicament for gene therapy of a disease or condition, wherein:

the composition comprises a delivery agent comprising a therapeutic nucleic acid molecule, and an agent that facilitates entry of the delivery agent into the parenchymal cells in a compartmentalized tissue or organ or portion of a tissue or organ;

the organ or tissue or portion thereof is the liver or a portion of the liver;

the delivery agent is a virus that comprises the therapeutic nucleic acid molecule;

the agent that facilitates entry into the parenchymal cells comprises a transcriptional enhancer of a virus-specific cell surface receptor;

the composition contains a single dose that is therapeutically effective for administration without dilution into the parenchyma of the liver or portion thereof that is to be compartmentalized for at least 25 minutes up to 1 hour following administration for quantitative uptake of the administered virus or viral vector;

a single dosage of the composition contains 1×10^3 to 1×10^{12} viral particles;

the nucleic acid molecule encodes an enzyme, a hormone, a coagulation or clotting factor, a cytokine, a growth factor or active portion thereof, an antibody or antigen binding portion thereof, an angiogenesis modulator, an immunomodulator, a pain modulator, a receptor or active portion thereof, a transport protein or a regulatory protein, for treating a disease or condition;

the disease or condition is selected from among arthritis, chronic pain, HIV-related AIDS, atherosclerosis, restenosis, inherited enzyme deficiency, inherited immune deficiency, cancer, a retrovirus infection, hemophilia, diabetes, a muscular dystrophy, a dystrophy, a cardiovascular disorder, cystic fibrosis, a neurodegenerative disorder, trauma, pain, sickle cell anemia, autoimmune disease, inflammatory disease and hypertension;

the composition is to be administered into the parenchyma of a compartmentalized tissue, organ, or portion of a tissue or organ sufficient in size to compartmentalize and for administration of the composition;

the parenchyma in the compartmentalized tissue or organ or portion thereof does not include connective tissue, blood vessels, nerves or ducts; and

a compartmentalized tissue or organ or portion of a tissue or organ is a tissue or organ that has been clamped to isolate it from the systemic circulation, whereby the arteries, veins, ducts and/or vessels servicing or traversing the tissue or organ or portion of the tissue or organ are blocked so that blood supply and flow to the tissue or organ or portion thereof is reduced or eliminated.

2. A composition for direct delivery of a therapeutic nucleic acid molecule into parenchyma cells of an organ or tissue for treatment of a disease or condition, comprising:

a delivery agent comprising a nucleic acid molecule that encodes an enzyme, a hormone, a coagulation or clotting factor, a cytokine, a growth factor or active portion thereof, an antibody or antigen binding portion thereof, an angiogenesis modulator, an immunomodulator, a pain modulator, a receptor or active portion thereof, a transport protein or a regulatory protein, for treating a disease or condition; and

an agent that facilitates entry of the delivery agent into the parenchymal cells in a compartmentalized tissue or organ or portion of a tissue or organ, wherein:

the delivery agent is a virus;

the composition comprises a transcriptional enhancer of a virus-specific cell surface receptor;

a therapeutically effective single dosage of the composition contains 1×10^3 to 1×10^{12} viral particles;

the composition is formulated for direct administration of the delivery agent comprising the nucleic acid molecule into the parenchyma of a compartmentalized tissue, organ, or portion of a tissue or organ sufficient in size to compartmentalize and for administration of the composition;

a compartmentalized tissue or organ or portion of a tissue or organ is a tissue or organ that has been isolated from the systemic circulation, whereby the arteries, veins, ducts and/or vessels servicing or traversing the tissue or organ or portion of the tissue or organ are blocked so that blood supply and flow to the tissue or organ or portion thereof is reduced or eliminated; and

the disease or condition is selected from among arthritis, chronic pain, HIV-related AIDS, atherosclerosis, restenosis, inherited enzyme deficiency, inherited immune deficiency, cancer, a retrovirus infection, hemophilia, diabetes, a muscular dystrophy, a dystrophy, a cardiovascular disorder, cystic fibrosis, a neurodegenerative disorder, trauma, pain, sickle cell anemia, autoimmune disease, inflammatory disease and hypertension.

3. The use of claim 1, wherein the therapeutic nucleic acid molecule encodes a polypeptide selected from among adenosine deaminase, cystic fibrosis transmembrane conductance regulator (CTFR), galsulfase, laronidase, N-acetylgalactosamine 6-sulfatase, phenylalanine ammonia lyase, acid alpha glucosidase, imiglucerase, alglucosidase alpha, thyrotropin, growth hormone, insulin, thyroid hormone, erythropoietin (EPO), interleukin-1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-7, interferons (IFN), tumor necrosis factor (TNF), IL-12, IL-18, fms-related tyrosine kinase 3 (flt3), neuropilin-2 (NP2), bone morphogenic protein (BMPs), epidermal growth factor (EGF), fibroblast growth factor (FGF), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), platelet derived growth factor (PDGF), transforming growth factor α and β, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), transforming growth factor receptor (TGFR), vascular endothelial growth factor receptor (VEGFR), plasminogen activator, urokinase, Factor VIII, Factor IX, von Willebrand factor, metalloproteinase thrombospondin motifs 1 (METH-1), METH-2, tryptophanyl-tRNA synthetase (TrpRS) fragments, proliferin-related protein, prolactin fragment, pigment epithelium derived growth factor (PEDF), vasostatin, angiostatin, endostatin, kininostatin, fibrinogen-E fragment, thrombospondin, tumstatin, canstatin, restin, soluble fms-like tyrosine kinase-1 (sFlt-1), soluble vascular endothelial growth factor receptors (sFlk), soluble Neuropilin I (sNRP1), Interferon gamma-induced protein 10 (IP-10), Platelet factor 4 (PF-4), Gro-beta, soluble Ephrin type-B receptor 4 (sEphB4), sephrinB2, TGF, IGF-1, herpes simplex virus thymidine kinase (HSV-TK), carboxypeptidase G2 (CPG2), carboxylesterase (CA), cytosine deaminase (CD), cytochrome P450 (cyt-450), deoxycytidine kinase (dCK), nitroreductase (NR), purine nucleoside phosphorylase (PNP), thymidine phosphorylase (TP), varicella zoster virus thymidine kinase (VZV-TK), xanthine-guanine phosphoribosyl transferase (XGPRT), Aspartylglucosaminidase, α-Galactosidase A, Palmitoyl Protein Thioesterase, Tripeptidyl Peptidase, Lysosomal transmembrane protein, cysteine transporter, Acid ceramidase, acid α-L-fucosidase, protective protein/cathepsin A, acid-β-glucosidase or glucocerebrosidase, acid β-galactosidase, iduronate-2-sulfatase, α-L-Iduronidase, galactocerebrosidase, acid α-mannosidase, acid β-mannosidase, arylsulfatase B, arylsulfatase

A, N-Acetylgalactosamine-6-sulfate sulfatase, N-Acetlylglucosamine-l-phosphotransferase, Acid sphingomyelinase, β-Hexosaminidase B, Heparan N-sulfatase, α-N-Acetylglucosaminidase, Acetyl-Co, α-glucosaminide N-acetyltransferase, N-Acetylglucosamine-6-sulfate sulfatase, β-Glucuronidase, acid lipase, neprilysin, the insulin-degrading enzyme insulysin, thimet oligopeptidase, calbindin D28, parvalbumin, hypoxia induced factor 1-alpha (HIF1-alpha), sirtuin-2 (SIRT-2), survival motor neuron protein-1 (SMN-1), SMN-2, glial cell-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNF), low density lipoprotein receptor (LDLR), lipoprotein lipase (LPL), Alpha-1-Antitrypsin (AAT), UDP-glucuronyl-transferase (UGT), UGT1A1, glucose-6 phosphatase, phosphoenolpyruvate-carboxykinase, galactose-1 phosphate uridyl transferase, phenylalanine hydroxylase, branched chain alpha-ketoacid dehydrogenase, fumarylacetoacetate hydrolase, methylmalonyl-CoA mutase, ornithine transcarbamylase, argininosuccinic acid synthetase, hypoxanthine guanine phosphoribosyl transferase, biotinidase, beta-glucocerebrosidase, porphobilinogen deaminase and p53.

4. The use of claim 1 or claim 3, wherein the disease or condition treatable by a therapeutic nucleic acid molecule is selected from among hemophilia, diabetes and an inborn error of metabolism.

5. The use of claim 1, wherein the therapeutic nucleic acid molecule encodes a polypeptide selected from among Factor VIII for treating hemophilia A; a Factor IX for treating hemophilia B; an insulin gene for treating type I diabetes mellitus; an alpha-1-antitrypsin (AAT) for treating alpha-1-antitrypsin (AAT) deficiency; a hemochromatosis protein (HFE) for treating hemochromatosis; a copper-transporting ATPase 2 for treating Wilson's disease; UDP glucuronosyltransferase 1A1 (UGT1A1) for treating Crigler-Najjar syndrome type I; ornithine transcarbamylase (OTC) for treating ornithine transcarbamylase deficiency, type II; low density lipoprotein receptor (LDLR) for treating familial hypercholesterolemia; fibrinogen alpha (FGA), beta (FGB) or gamma (FGG) for treating afibrinogenemia; glucose-6-phosphate-α for treating glycogen storage disease (GSD) type Ia; G6PT for treating GSD type Ib; acid-α-glucosidase for treating GSD type II (Pompe); α-L-iduronidase for treating mucopolysaccharidosis (MPSI); sulphamidase for treating MPS IIIA; α-N-acetylglucosaminidase (NaGlu) for treating MPS IIIB; β-glucuronidase for treating MPS VII; α-galactosidase A for treating Fabry disease; glucocerebrosidase for treating Gaucher's disease; acid sphingomyelinase for treating Niemann-Pick syndrome; phenylalanine hydroxylase for treating phenylketonuria; TIMP antagonist or anti-HSC molecules for treating liver fibrosis; anti-ROS molecules for treating liver ischemia reperfusion injury; the amyloid-beta degrading enzyme neprilysin, the insulin-degrading enzyme insulysin, or thimet oligopeptidase for treating Alzheimer's disease; insulin growth factor-1 (IGF-1), calbindin D28, parvalbumin, hypoxia induced factor 1-alpha (HIF1-alpha), sirtuin-2 (SIRT-2), survival motor neuron protein-1 (SMN-1), SMN-2, glial cell-derived neurotrophic factor (GDNF) or ciliary neurotrophic factor (CNF) for treating Amyotrophic Lateral Sclerosis (ALS); galactose-1 phosphate uridyl transferase for treating galactosemia; branched chain alpha-ketoacid dehydrogenase for treating maple syrup urine disease; fumarylacetoacetate hydrolase for treating tyrosinemia type 1; methylmalonyl-CoA mutase for treating methylmalonic acidemia; argininosuccinic acid synthetase for treating citrullinemia; hypoxanthine guanine phosphoribosyl transferase for treating Gout and Lesch Nyhan syndrome; beta-glucuronidase for treating Sly syndrome; peroxisome membrane protein 70 kDa for treating Zellweger syndrome; enfuvirtide for treating Human immunodeficiency virus (HIV) infection; adenosine deaminase (ADA) for treating combined immunodeficiency disease (SCID); CFTR for treating cystic fibrosis; porphobilinogen deaminase (PBDG) for treating acute intermittent porphyria; interferon-beta for treating multiple sclerosis;

lipoprotein lipase for treating lipoprotein lipase deficiency (LPLD); p53 for treating cancer; and glutamic acid decarboxylase (GAD) for treating Parkinson's Disease.

6. The use of any of claims 1 and 3-5, wherein the compartmentalized tissue or organ or portion of a tissue or organ to which the composition is to be administered is parenchymally clamped to cut off the blood supply and flow through the tissue or organ or portion thereof.

7. The use of claim 1, wherein the compartmentalized portion of the liver is selected from among a lobe, a segment or a portion of a lobe, and a segment of the liver.

8. The use of claim 7, wherein the lobe or portion of a lobe is selected from among the right lobe, the left lobe, the quadrate lobe and the caudate lobe, and portions thereof.

9. The use of any of claims 1 and 3-8, wherein the virus is selected from among an adenovirus, an adeno-associated virus (AAV), a retrovirus, a vaccinia virus and a herpes simplex virus.

10. The use of any of claims 1 and 3-9, wherein:

the composition is formulated for direct administration of the delivery agent comprising the nucleic acid molecule into the parenchyma of a compartmentalized liver or portion of a liver sufficient in size to compartmentalize and to effect administration of the composition; and

the composition comprises a delivery agent that is an adenovirus or adeno-associated virus vector comprising the therapeutic nucleic acid molecule, wherein the nucleic acid molecule is heterologous to the virus genome.

11. The use of claim 9 or claim 10, wherein the virus is an adenovirus and the serotype of the adenovirus is adenovirus type 2 or adenovirus type 5.

12. The use of any of claims 1 and 3-11, wherein the composition contains lipids or polymer reagents that facilitate entry into parenchymal cells.

13. The use of any of claims 1 and 3-12, wherein the transcriptional enhancer is a histone deacetylase (HDAC) inhibitor.

14. The use of any of claims 1, 3-10, 12 and 13, wherein the delivery agent is an adenovirus or adeno-associated virus comprising a heterologous nucleic acid molecule in its genome.

15. The use of any of claims 1 and 3-14, wherein the composition comprises a further agent that facilitates uptake or entry into parenchymal cells selected from among polyamine, calcium phosphate precipitate, histone protein, protamine, polyethylenimine, polylysine, polyarginine, polyornithinine, DEAE dextran, polybrene, polyampholyte complex, spermine, spermidine, putrescine, human serum albumin, DNA binding proteins, non-histone chromosomal proteins, coat proteins from DNA viruses and polymers of N-substituted glycines.

16. The composition of claim 2, wherein the therapeutic nucleic acid molecule encodes a polypeptide selected from among adenosine deaminase, cystic fibrosis transmembrane conductance regulator (CTFR), galsulfase, laronidase, N-acetylgalactosamine 6-sulfatase, phenylalanine ammonia lyase, acid alpha glucosidase, imiglucerase, alglucosidase alpha, thyrotropin, growth hormone, insulin, thyroid hormone, erythropoietin (EPO), interleukin-1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-7, interferons (IFN), tumor necrosis factor (TNF), IL-12, IL-18, fms-related tyrosine kinase 3 (flt3), neuropilin-2 (NP2), bone

morphogenic protein (BMPs), epidermal growth factor (EGF), fibroblast growth factor (FGF), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), platelet derived growth factor (PDGF), transforming growth factor α and β, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), transforming growth factor receptor (TGFR), vascular endothelial growth factor receptor (VEGFR), plasminogen activator, urokinase, Factor VIII, Factor IX, von Willebrand factor, metalloproteinase thrombospondin motifs 1 (METH-1), METH-2, tryptophanyl-tRNA synthetase (TrpRS) fragments, proliferin-related protein, prolactin fragment, pigment epithelium derived growth factor (PEDF), vasostatin, angiostatin, endostatin, kininostatin, fibrinogen-E fragment, thrombospondin, tumstatin, canstatin, restin, soluble fms-like tyrosine kinase-1 (sFlt-1), soluble vascular endothelial growth factor receptors (sFlk), soluble Neuropilin I (sNRP1), Interferon gamma-induced protein 10 (IP-10), Platelet factor 4 (PF-4), Gro-beta, soluble Ephrin type-B receptor 4 (sEphB4), sephrinB2, TGF, IGF-1, herpes simplex virus thymidine kinase (HSV-TK), carboxypeptidase G2 (CPG2), carboxylesterase (CA), cytosine deaminase (CD), cytochrome P450 (cyt-450), deoxycytidine kinase (dCK), nitroreductase (NR), purine nucleoside phosphorylase (PNP), thymidine phosphorylase (TP), varicella zoster virus thymidine kinase (VZV-TK), xanthine-guanine phosphoribosyl transferase (XGPRT), Aspartylglucosaminidase, α-Galactosidase A, Palmitoyl Protein Thioesterase, Tripeptidyl Peptidase, Lysosomal transmembrane protein, cysteine transporter, Acid ceramidase, acid α-L-fucosidase, protective protein/cathepsin A, acid-β-glucosidase or glucocerebrosidase, acid β-galactosidase, iduronate-2-sulfatase, α-L-Iduronidase, galactocerebrosidase, acid α-mannosidase, acid β-mannosidase, arylsulfatase B, arylsulfatase A, N-Acetylgalactosamine-6-sulfate sulfatase, N-Acetylglucosamine-l-phosphotransferase, Acid sphingomyelinase, β-Hexosaminidase B, Heparan N-sulfatase, α-N-Acetylglucosaminidase, Acetyl-CoA, α-glucosaminide N-acetyltransferase, N-Acetylglucosamine-6-sulfate sulfatase, β-Glucuronidase, acid lipase, neprilysin, the insulin-degrading enzyme insulysin, thimet oligopeptidase, calbindin D28, parvalbumin, hypoxia induced factor 1-alpha (HIF1-alpha), sirtuin-2 (SIRT-2), survival motor neuron protein-1 (SMN-1), SMN-2, glial cell-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNF), low density lipoprotein receptor (LDLR), lipoprotein lipase (LPL), Alpha-1-Antitrypsin (AAT), UDP-glucuronyl-transferase (UGT), UGT1A1, glucose-6 phosphatase, phosphoenolpyruvate-carboxykinase, galactose-1 phosphate uridyl transferase, phenylalanine hydroxylase, branched chain alpha-ketoacid dehydrogenase, fumarylacetoacetate hydrolase, methylmalonyl-CoA mutase, ornithine transcarbamylase, argininosuccinic acid synthetase, hypoxanthine guanine phosphoribosyl transferase, biotinidase, beta-glucocerebrosidase, porphobilinogen deaminase and p53.

17. The composition of claim 2 or claim 16, wherein the disease or condition treatable by the therapeutic nucleic acid molecule is selected from among hemophilia, diabetes and an inborn error of metabolism.

18. The composition of claim 2, wherein the therapeutic nucleic acid molecule encodes a polypeptide selected from among Factor VIII for treating hemophilia A; a Factor IX for treating hemophilia B; an insulin gene for treating type I diabetes mellitus; an alpha-1-antitrypsin (AAT) for treating alpha-1-antitrypsin (AAT) deficiency; a hemochromatosis protein (HFE) for treating hemochromatosis; a copper-transporting ATPase 2 for treating Wilson's disease; UDP glucuronosyltransferase 1A1 (UGT1A1) for treating Crigler-Najjar syndrome type I; ornithine transcarbamylase (OTC) for treating ornithine transcarbamylase deficiency, type II; low density lipoprotein receptor (LDLR) for treating familial

hypercholesterolemia; fibrinogen alpha (FGA), beta (FGB) or gamma (FGG) for treating afibrinogenemia; glucose-6-phosphate-α for treating glycogen storage disease (GSD) type Ia; G6PT for treating GSD type Ib; acid-α-glucosidase for treating GSD type II (Pompe); α-L-iduronidase for treating mucopolysaccharidosis (MPSI); sulphamidase for treating MPS IIIA; α-N-acetylglucosaminidase (NaGlu) for treating MPS IIIB; β-glucuronidase for treating MPS VII; α-galactosidase A for treating Fabry disease; glucocerebrosidase for treating Gaucher's disease; acid sphingomyelinase for treating Niemann-Pick syndrome; phenylalanine hydroxylase for treating phenylketonuria; TIMP antagonist or anti-HSC molecules for treating liver fibrosis; anti-ROS molecules for treating liver ischemia reperfusion injury; the amyloid-beta degrading enzyme neprilysin, the insulin-degrading enzyme insulysin, or thimet oligopeptidase for treating Alzheimer's disease; insulin growth factor-1 (IGF-1), calbindin D28, parvalbumin, hypoxia induced factor 1-alpha (HIF1-alpha), sirtuin-2 (SIRT-2), survival motor neuron protein-1 (SMN-1), SMN-2, glial cell-derived neurotrophic factor (GDNF) or ciliary neurotrophic factor (CNF) for treating Amyotrophic Lateral Sclerosis (ALS); galactose-1 phosphate uridyl transferase for treating galactosemia; branched chain alpha-ketoacid dehydrogenase for treating maple syrup urine disease; fumarylacetoacetate hydrolase for treating tyrosinemia type 1; methylmalonyl-CoA mutase for treating methylmalonic acidemia; argininosuccinic acid synthetase for treating citrullinemia; hypoxanthine guanine phosphoribosyl transferase for treating Gout and Lesch Nyhan syndrome; beta-glucuronidase for treating Sly syndrome; peroxisome membrane protein 70 kDa for treating Zellweger syndrome; enfuvirtide for treating Human immunodeficiency virus (HIV) infection; adenosine deaminase (ADA) for treating combined immunodeficiency disease (SCID); CFTR for treating cystic fibrosis; porphobilinogen deaminase (PBDG) for treating acute intermittent porphyria; interferon-beta for treating multiple sclerosis; lipoprotein lipase for treating lipoprotein lipase deficiency (LPLD); p53 for treating cancer; and glutamic acid decarboxylase (GAD) for treating Parkinson's Disease.

19. The composition of any of claims 2 and 16-18, wherein the compartmentalized tissue or organ or portion of a tissue or organ to which the composition is to be administered is parenchymally clamped to cut off the blood supply and flow through the tissue or organ or portion thereof.

20. The composition of any of claims 2 and 16-19, wherein the composition is to be administered by injection into the parenchyma of a compartmentalized liver or a portion of the liver.

21. The composition of claim 20, wherein the compartmentalized portion of the liver is selected from among a lobe, a segment or a portion of a lobe, and a segment of the liver.

22. The composition of claim 21, wherein the lobe or portion of a lobe is selected from among the right lobe, the left lobe, the quadrate lobe and the caudate lobe, and portions thereof.

23. The composition of any of claims 2 and 16-22, wherein the virus is selected from among an adenovirus, an adeno-associated virus (AAV), a retrovirus, a vaccinia virus and a herpes simplex virus.

24. The composition of any of claims 2 and 16-22, wherein:

the composition is formulated for direct administration of the delivery agent comprising the nucleic acid molecule into the parenchyma of a compartmentalized liver or portion of a liver sufficient in size to compartmentalize and to effect administration of the composition; and

the composition comprises a delivery agent that is an adenovirus or adeno-associated virus vector comprising the therapeutic nucleic acid molecule, wherein the nucleic acid molecule is heterologous to the virus genome.

25. The composition of claim 23 or claim 24, wherein the virus is an adenovirus and the serotype of the adenovirus is adenovirus type 2 or adenovirus type 5.

26. The composition of any of claims 2 and 16-25, wherein the nucleic acid molecule is selected from among a DNA molecule or an RNA molecule.

27. The composition of any of claims 2 and 16-26, wherein the transcriptional enhancer is a histone deacetylase (HDAC) inhibitor.

28. The composition of any of claims 2, 16-24, 26 and 27, wherein:

the delivery agent is an adenovirus or adeno-associated virus comprising a heterologous nucleic acid molecule in its genome;

the composition is for single dosage administration; and

the amount of adenovirus in the composition is less than 1×10^7 viral particles.