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, there is provided a use ~~of a composition in the manufacture of a medicament for treating a disease or condition treatable by a therapeutic nucleic acid, wherein: the composition comprises a delivery agent comprising the therapeutic nucleic acid molecule; 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; the parenchyma in the compartmentalized tissue or organ or portion thereof does not include connective tissue, blood vessels, nerves or ducts; the compartmentalized tissue or organ or portion of a tissue or organ is 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 treatable by a therapeutic nucleic acid is selected from among a genetic deficiency, a disease or condition ameliorated by an exogenous gene product, and a disease or condition involving aberrant or altered expression of a gene product in its etiology~~ of a composition in the manufacture of a medicament for treating disease or condition by introducing nucleic acid into cells of an organ or tissue, wherein:

the disease or condition is diabetes;

the composition comprises:

a delivery agent comprising nucleic acid encoding an insulin; 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

the composition is formulated for use without dilution in the parenchyma cells of a compartmentalized tissue, organ, or portion of a tissue or organ; and

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 by clamping the tissue, organ or portion thereof, 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 ~~second~~ aspect, there is provided a ~~composition for direct delivery of a therapeutic nucleic acid molecule to parenchyma cells, comprising: a delivery agent comprising a therapeutic nucleic acid molecule, wherein the nucleic acid is a therapeutic or encodes a therapeutic protein; and an agent to facilitate entry into the parenchymal cells, wherein the composition is formulated for direct administration of the delivery agent into the parenchyma of a compartmentalized tissue, organ, or portion of a tissue or organ sufficient in size to compartmentalize and to for administration of the composition~~composition for delivery of nucleic acid encoding an insulin into parenchyma cells of an organ or tissue for treatment of diabetes , comprising:

a delivery agent comprising a nucleic acid molecule that encodes insulin; and

lipids or polymer reagents that facilitate entry into parenchymal cells,

wherein the concentration of delivery agent and reagents is for use in parenchymal cells in an organ or tissue without dilution.

~~In another aspect, there is provided a use of compartmentalization and direct parenchymal administration into a tissue, organ or portion of an organ for treatment of a genetic disease or condition for delivery of a composition comprising a therapeutic nucleic acid that treats the disease or condition into the parenchyma the tissue, organ or portion thereof.~~

In another aspect, 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 without dilution and contains less than 1×10^7 viral particles or less than 1×10^7 pfu of the virus; and

the composition comprises and agent that facilitates uptake by or entry into parenchymal cells.

In another aspect, there is provided a composition, comprising:

an adenovirus vector or an adeno-associated virus vector comprising nucleic acid encoding insulin in its genome, wherein the amount of adenovirus or adeno-associated virus in the composition is less than1×10^8 particles or less than 1×10^8 pfu, 1×10^7 pfu, 1×10^6 pfu, 1×10^5 pfu, 1×10^4 pfu or 1×10^3 pfu; and

a histone deacetylase (HDAC) inhibitor.

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; and

an agent that facilitates entry of the delivery agent into the parenchymal cells;

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 formulated for direct 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 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

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 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 encoded polypeptide is 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, growth hormone, 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, Niemann-Pick disease type Cl (NPC-l), 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), liproprotein 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, adenosine deaminase, hyposanthine guanine phosphoribosyl transferase, biotinidase, beta-glucocerebrosidase, beta-glucuronidase, porphobilinogen deaminase and p53.

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

5. The use of any of claims 1, and 3 , 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; 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; hyposanthine guanine phosphoribosyl transferase for treating Gout and Lesch Nyan 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 or composition of any of claims 1 and 3-6 , wherein the tissue or organ or portion of the tissue or organ is selected from among the liver, brain, spinal cord,

pancreas, heart, skin, kidney, lung, blood vessel, bone, muscle, uterus, cervix, prostate, urethra, and intestine.

8. The use of any of claims 1and 3-7, wherein the composition is to be administered by direct administration to the parenchyma of a compartmentalized liver or a portion of the liver.

9. The use of claim 8, wherein the compartmentalized portion of the liver is selected from among a lobe, segment or a portion of a lobe and a segment of the liver.

10. The use of claim 9, 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 portion thereof.

11. The use of any of claims 1 and 3-10, wherein the delivery agent is selected from among a single stranded DNA, a linear stranded DNA, a viral vector, a circular DNA, a non-viral vector, a virus, a virus-like particle, a minicircle, a nanoparticle that comprises the nucleic acid molecule, and a whole cell that comprises the nucleic acid molecule.

12. The use of claim 11, wherein the delivery agent is a non-viral vector and the non-viral vector is an expression vector.

13. The use of claim 11, wherein the delivery agent is a nanoparticle and the nanoparticle is targeted or radiolabeled.

14. The use of any of claims 1and 3-11, wherein the delivery agent is a virus.

15. The use of claim 14, wherein the virus is selected from among an adenovirus, an adeno-associated virus (AAV), a retrovirus, a vaccinia virus and a herpes simplex virus.

16. The use of any of claims 1 and 3-15, 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.

17. The use of claim 15 or claim 16, wherein the virus is an adenovirus and the serotype of the adenovirus is adenovirus type 2 or adenovirus type 5.

18. The use of any of claims 1 and 3-14, wherein the nucleic acid molecule is selected from among a DNA molecule or a RNA molecule.

19. The use of any of claims 1 and 3-18, wherein the delivery agent is formulated with lipids or polymer reagents that facilitate entry into parenchymal cells.

20. The use of any of claims 1 and 3-19, wherein the delivery agent is formulated with an agent that promotes cellular uptake of the delivery agent.

21. The use of any of claims 1-and 3-18, wherein the delivery agent is a virus and the composition comprises a transcriptional enhancer of a virus-specific cell surface receptor.

22. The use of claim 21, wherein the transcriptional enhancer is a histone deacetylase (HDAC) inhibitor.

23. The use of any of claims 1 and 3-22, 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 than1 x 10^7 particles or less than 1 x 10^7 pfu, 1 x 10^6 pfu, 1 x 10^5 pfu, 1 x 10^4 pfu, 1 x 10^3 pfu.

24. The use of any of claims 1 and 3-13, wherein the composition comprises an 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.

25. 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 x 10^7 viral particles or less than 1 x 10^7 pfu of the virus; and

the composition comprises and agent that facilitates uptake by or entry into parenchymal cells.

26. The composition of claim 24, wherein the agent that facilitates uptake or entry is 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.

27. The use of claim 26, wherein the agent is a histone deacetylase (HDAC) inhibitor.

28. The composition of claim 2, wherein the encoded polypeptide is 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, growth hormone, 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, Niemann-Pick disease type Cl (NPC-l), 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, adenosine deaminase, hyposanthine guanine phosphoribosyl transferase, biotinidase, beta-glucocerebrosidase, beta-glucuronidase, porphobilinogen deaminase and p53.

29. The composition of claim 2 or claim 28 , wherein the disease or condition treatable by a therapeutic nucleic acid is selected from among hemophilia, diabetes and an inborn error of metabolism.

30. The composition of any of claims 2, and 29 , 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 1 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; 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; hyposanthine guanine phosphoribosyl transferase for treating Gout and Lesch Nyan 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.

31. The composition of any of claims 2 and 28-30, 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.

32. The use or composition of any of claims 2 and 28-31, wherein the tissue or organ or portion of the tissue or organ is selected from among the liver, brain, spinal cord, pancreas, heart, skin, kidney, lung, blood vessel, bone, muscle, uterus, cervix, prostate, urethra, and intestine.

33. The composition of any of claims 2 and 28-32, wherein the composition is to be administered by direct administration to the parenchyma of a compartmentalized liver or a portion of the liver.

34. The composition of claim 33, wherein the compartmentalized portion of the liver is selected from among a lobe, segment or a portion of a lobe and a segment of the liver.

35. The composition of claim 34, 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 portion thereof.

36. The composition of any of claims 2 and 28-35, wherein the delivery agent is selected from among a single stranded DNA, a linear stranded DNA, a viral vector, a circular DNA, a non-viral vector, a virus, a virus-like particle, a minicircle, a nanoparticle that comprises the nucleic acid molecule, and a whole cell that comprises the nucleic acid molecule.

37. The composition of claim 36, wherein the delivery agent is a non-viral vector and the non-viral vector is an expression vector.

38. The composition of claim 36, wherein the delivery agent is a nanoparticle and the nanoparticle is targeted or radiolabeled.

39. The composition of any of claims 3 and 28-36, wherein the delivery agent is a virus.

40. The composition of claim 39, wherein the virus is selected from among an adenovirus, an adeno-associated virus (AAV), a retrovirus, a vaccinia virus and a herpes simplex virus.

41. The composition of any of claims 2 and 28-40, 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.

42. The composition of claim 40 or claim 41, wherein the virus is an adenovirus and the serotype of the adenovirus is adenovirus type 2 or adenovirus type 5.

43. The composition of any of claims 2 and 28-39, wherein the nucleic acid molecule is selected from among a DNA molecule or a RNA molecule.

44. The composition of any of claims 2 and 28-43, wherein the delivery agent is formulated with lipids or polymer reagents that facilitate entry into parenchymal cells.

45. The composition of any of claims 2 and 28-43, wherein the delivery agent is formulated with an agent that promotes cellular uptake of the delivery agent.

46. The composition of any of claims 2-and 28-45, wherein the delivery agent is a virus and the composition comprises a transcriptional enhancer of a virus-specific cell surface receptor.

47. The composition of claim 46, wherein the transcriptional enhancer is a histone deacetylase (HDAC) inhibitor.

48 The composition of any of claims 2 and 28-47, 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 than1 x 10^7 particles or less than 1 x 10^7 pfu, 1 x 10^6 pfu, 1 x 10^5 pfu, 1 x 10^4 pfu, 1 x 10^3 pfu.

49. The composition of any of claims 2 and 28-48, wherein the composition comprises an 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.

Claims

1. Use of a composition in the manufacture of a medicament for treating disease or condition by introducing nucleic acid into cells of an organ or tissue, wherein:

the disease or condition is diabetes;

the composition comprises:

a delivery agent comprising nucleic acid encoding an insulin; 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

the composition is formulated for use without dilution in the parenchyma cells of a compartmentalized tissue, organ, or portion of a tissue or organ; and

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 by clamping the tissue, organ or portion thereof, 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 delivery of nucleic acid encoding an insulin into parenchyma cells of an organ or tissue for treatment of diabetes , comprising:

a delivery agent comprising a nucleic acid molecule that encodes insulin; and

lipids or polymer reagents that facilitate entry into parenchymal cells,

wherein the concentration of delivery agent and reagents is for use in parenchymal cells in an organ or tissue without dilution.

3. The use of claim 1, wherein the tissue or organ or portion of a tissue or organ is clamped to cut off the blood supply and flow through the tissue or organ or portion thereof.

4. The use of claim 1, wherein the tissue or organ or portion of the tissue or organ is selected from among the liver, brain, spinal cord, pancreas, heart, skin, kidney, lung, blood vessel, bone, muscle, uterus, cervix, prostate, urethra, and intestine.

5. The use of claim 1, wherein the tissue or organ or portion thereof that is compartmentalized is the liver or a portion of the liver.

6. The use of claim 5, wherein the compartmentalized portion of the liver is selected from among a lobe, segment or a portion of a lobe and a segment of the liver.

7. The use of claim 6, 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 portion thereof.

8. The use of any of claims 1 and 3-7, wherein the delivery agent is selected from among a single stranded DNA, a linear stranded DNA, a viral vector, a circular DNA, a non-viral vector, a virus, a virus-like particle, a minicircle, a nanoparticle that comprises the nucleic acid molecule, and a whole cell that comprises the nucleic acid molecule.

9. The use of claim 8, wherein the delivery agent is a non-viral vector and the non-viral vector is an expression vector.

10. The use of claim 8, wherein the delivery agent is a nanoparticle and the nanoparticle is targeted or radiolabeled.

11. The use of any of claims 1and 3-8, wherein the delivery agent is a viral vector.

12. The use of claim 11, wherein the viral vector is selected from among an adenovirus, an adeno-associated virus (AAV), a retrovirus, a vaccinia virus and a herpes simplex virus.

13. The use of any of claims 1 and 3-12, wherein:

the composition is formulated for use without dilution of the delivery agent comprising the nucleic acid molecule into the parenchyma of a compartmentalized liver or portion of a liver; and

the composition comprises a delivery agent that is an adenovirus or adeno-associated virus vector comprising the nucleic acid encoding the insulin.

14. The use of claim 12 or claim 13, wherein the virus is an adenovirus and the serotype of the adenovirus is adenovirus type 2 or adenovirus type 5.

15. The use of any of claims 1 and 3-11, wherein the nucleic acid molecule is selected from among a DNA molecule or a RNA molecule.

16. The use of any of claims 1 and 3-15, wherein the delivery agent is formulated with lipids or polymer reagents that facilitate entry into parenchymal cells.

17. The use of any of claims 1 and 3-16, wherein the delivery agent is formulated with an agent that promotes cellular uptake of the delivery agent.

18. The use of any of claims 1-and 3-15, wherein the delivery agent is a virus and the composition comprises a transcriptional enhancer of a virus-specific cell surface receptor.

19. The use of claim 18, wherein the transcriptional enhancer is a histone deacetylase (HDAC) inhibitor.

20. The use of any of claims 1 and 3-19, wherein:

the delivery agent is an adenovirus or adeno-associated virus comprising nucleic acid encoding an insulin in its genome;

the composition is for use without dilution; and

the amount of adenovirus in the composition is less than1 x 10^8 particles or less than 1 x 10^8 pfu, 1 x 10^7 pfu, 1 x 10^6 pfu, 1 x 10^5 pfu, 1 x 10^4 pfu, or 1 x 10^3 pfu.

21. The use of any of claims 1 and 3-20, wherein the composition comprises an agent that facilitates uptake or entry into parenchymal cells selected from among polyamine, calcium phosphate precipitate, protamine, polyethyleneimine, polylysine, polyarginine, polyornithinine, DEAE dextran, polyampholyte complex, spermine, spermidine, putrescine, and human serum albumin.

22. The composition of claim 2, wherein the delivery agent is a viral vector, and the composition comprises a transcriptional enhancer of a virus-specific cell surface receptor.

23. The composition of claim 22, wherein the transcriptional enhancer is a histone deacetylase (HDAC) inhibitor.

24. The composition of claim 22, wherein the agent that facilitates uptake or entry into parenchymal cells selected from among calcium phosphate precipitate, protamine, polyethylenimine, polylysine, polyarginine, polyornithinine, DEAE dextran, spermine, spermidine, putrescine and human serum albumin.

25. A composition, comprising an adenovirus or adeno-associated virus comprising heterologous nucleic acid in its genome, wherein:

the composition is formulated for without dilution and contains less than 1 x 10^7 viral particles or less than 1 x 10^7 pfu of the virus; and

the composition comprises and agent that facilitates uptake by or entry into parenchymal cells.

26. The composition of claim 25, wherein the agent that facilitates uptake or entry is selected from among calcium phosphate precipitate, protamine, polyethylenimine, polylysine, polyarginine, polyornithinine, DEAE dextran, spermine, spermidine, putrescine and human serum albumin.

27. The composition of claim 26, wherein the agent is a histone deacetylase (HDAC) inhibitor.

28. The composition of any of claims 2 and 22-27, wherein:

the delivery agent is an adenovirus or adeno-associated virus comprising nucleic acid encoding insulin in its genome;

the composition is for use without dilution; and

the amount of adenovirus or adeno-associated virus in the composition is less than1 x 10^8 particles or less than 1 x 10^8 pfu, 1 x 10^7 pfu, 1 x 10^6 pfu, 1 x 10^5 pfu, 1 x 10^4 pfu or 1 x 10^3 pfu.

29. A composition, comprising:

an adenovirus vector or an adeno-associated virus vector comprising nucleic acid encoding insulin in its genome, wherein the amount of adenovirus or adeno-associated virus in the composition is less than1 x 10^8 particles or less than 1 x 10^8 pfu, 1 x 10^7 pfu, 1 x 10^6 pfu, 1 x 10^5 pfu, 1 x 10^4 pfu or 1 x 10^3 pfu; and

a histone deacetylase (HDAC) inhibitor.

30. The composition of claim 29 for use for gene therapy for treating diabetes.