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 the use of a composition for manufacture of a medicament for treating a disease or condition treatable by a therapeutic nucleic acid molecule, wherein: the composition comprises a delivery agent comprising the therapeutic nucleic acid molecule; the composition is formulated as suitable for injection 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 to effect administration of the composition; the organ or tissue is a liver or portion of the liver; the delivery agent is a virus that comprises the therapeutic nucleic acid; composition contains 1×10^3 to 1×10^{12} viral particles; the composition contains a therapeutic single dose of the virus; the amount of delivery agent in the composition is at least 100-fold less than the amount of the same delivery agent in a composition formulated for intravenous administration for treatment of the same disease or condition in the same subject; the parenchyma of a compartmentalized tissue, organ or portion thereof does not include connective tissue, blood vessels, nerves or ducts; 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; the compartmentalized tissue or organ or portion of a tissue or organ is isolated from the systemic circulation, wherein the organ is clamped 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 compartmentalization is maintained for at least 25 minutes, whereby the uptake of the delivery agent by the parenchyma is quantitative.

CLAIMS

1. Use of a composition for manufacture of a medicament for treating a disease or condition treatable by a therapeutic nucleic acid molecule, wherein:

the composition comprises a delivery agent comprising the therapeutic nucleic acid molecule;

the composition is formulated as suitable for injection 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 to effect administration of the composition;

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

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

composition contains 1×10^3 to 1×10^{12} viral particles;

the composition contains a therapeutic single dose of the virus;

the amount of delivery agent in the composition is at least 100-fold less than the amount of the same delivery agent in a composition formulated for intravenous administration for treatment of the same disease or condition in the same subject;

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

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;

the compartmentalized tissue or organ or portion of a tissue or organ is isolated from the systemic circulation, wherein the organ is clamped 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

compartmentalization is maintained for at least 25 minutes, whereby the uptake of the delivery agent by the parenchyma is quantitative.

2. The use claim 1 , wherein the therapeutic nucleic acid molecule effects treatment of a disease or condition.

3. The use of claim 1 or claim 2, wherein the nucleic acid molecule encodes a polypeptide.

4. The use of claim 3, wherein the encoded polypeptide is selected from among an enzyme, a hormone, a coagulation or clotting factor, a cytokine, a growth factor or active portion thereof, an antibody or antigen portion thereof, an angiogenesis modulator, an immunomodulator, a pain modulator, a receptor or active portion thereof, a transport protein, a regulatory protein, an antigen and an allergen.

5. The use of claim 3 or claim 4, 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), erythropoietin (EPO), 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 1 (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-1-phosphotransferase, Acid sphingomyelinase, Niemann-Pick disease, type C1 (NPC-1), β-Hexosaminidase B, Heparan N-sulfatase,α-N-Acetylglucosaminidase, Acetyl-CoA:αglucosamininde 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-gluronidase, porphobilinogen deaminase and p53.

6. The use of any of claims 1-5, wherein the disease or condition treatable by a therapeutic nucleic acid 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 cardiovascular disorder, cystic fibrosis, a neurodegenerative disorder, trauma, pain, sickle cell anemia, autoimmune disease, inflammatory disease, and hypertension.

7. The use of any of claims 1-6, 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 (FGB) 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-gluronidase 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 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.

8. The use of any of claims 1-7, wherein the delivery agent is a retrovirus.

9. The use of any of claims 1-8 wherein the tissue or organ a portion of the liver.

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

11. The use of claim 10, 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 or portion thereof.

12. The use of any of claims 1-11, wherein the delivery agent is a lentivirus.

13. The use of any of claims 1-11, wherein the delivery agent is an adeno-associated virus.

14. The use of any of claims 1-11 claim , wherein the delivery agent is a virus selected from among an adenovirus, an adeno-associated virus (AAV), a retrovirus, vaccinia virus and herpes simplex virus.

15. The use of any of claims 1-11, wherein the virus is an adenovirus.

16. The use of any of claims 1-11, wherein:

the organ or portion thereof is the liver; and

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

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

18. The use of any of claims 15-17, wherein the adenovirus comprises a deletion in an E1, E2a, E2b, E3, or E4 coding region.

19. The use of any of claims 15-17, wherein the adenovirus comprises a deletion in the E1 coding region.

20. The use of any of claims 1-19, wherein the nucleic agent molecule is selected from among a DNA molecule, a RNA molecule, and an aptamer.

21. The use of claim 20, wherein the therapeutic nucleic acid molecule is selected from the among a microRNA, a small interfering RNA, a ribozyme and an antisense nucleic acid.

22. The use of any of claims 1-21, wherein the delivery agent is formulated with lipids or polymer reagents that facilitate entry by parenchymal cells.

23. The use of any of claims 1-22, wherein the delivery agent is formulated with an agent that promotes cellular uptake of the delivery agent.

24. The use of claim 23, wherein the delivery agent is a virus and the agent that promotes cellular uptake is a transcriptional enhancer of a virus-specific cell surface receptor.

25. The use of claim 24, wherein the agent is a histone deacetylase (HDAC) inhibitor.

26. The use of claim 25, wherein the HDAC inhibitor is selected from among trischostatin A, vorinostat (SAHA), belionostat (PXD101), LAQ824, panobinostat (LBH589), entinostat (MS-275), C199, mocetinostat (MGCD0103), romidepsin (lstodax), valproic acid, PCI-24781, SB939, resminostat, givinostat, CUDC-101, AR-42, CHR-2845, CHR-3996, 4SC-202, CG200745, Kevetrin, and trichostatin A (TSA).

27. The use of any of claims 1-26, wherein the amount of delivery agent in the composition at least 200-fold less than the amount of the same delivery agent in a composition formulated for intravenous administration for the same purpose in the same subject.

28. The use of claim 27, wherein the amount of delivery agent in the composition is at least 500-fold, 1000-fold, 5000-fold, or 10000-fold less than the amount of the same delivery agent in a composition formulated for intravenous administration.

29. The use of any of claims 1-11 and 13 and 17-28, wherein:

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

the amount of adenovirus in the composition is between 2×10^3 particles/mL to 1×10^{14} particles/mL, 2×10^3 particles/ mL to 1×10^{12} particles/mL, 2×10^3 particles/mL to 2×10^{11} particles/mL, 1×10^4 particles/mL to 5×10^{11} particles/mL, 1×10^5 particles/mL to 1×10^{11} particles/mL, 2×10^6 particles/mL to 2×10^{10} particles/mL, or 1×10^8 to 1×10^{10} particles/mL.

30. The use of any of claims 1-29, wherein the volume of the composition is or is between 0.02 mL to 100 mL, 0.05 mL to 50 mL, 1 mL to 10 mL, 0.05 mL to 5 mL or 0.02 mL to 1 mL.

31. The use of any of claims 1-11 and 17-30, wherein:

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

the composition is for single dosage administration; and

the amount of adenovirus in the composition is between less than 1×10^{11} particles, 1×10^{10} particles, 1×10^{9} particles, 1×10^{8} particles, 1×10^{7} particles, 1×10^{6} particles, 1×10^{5} particles, 1×10^{4} particles, or less.

32. The use of any of claims 1-31 wherein the amount of delivery agent is suitable for administration to a human patient.

33. The use of any of claims 1-32, wherein the amount of delivery agent is suitable for administration to a human child under the age of 18.

34. The use of any of claims 1-32, wherein the amount of delivery agent in the composition is suitable for administration to a fetus.