stranded DNA (ceDNA)) presents additional challenges relative to the smaller and/or flexible cargos (*e.g.*, siRNA). One such challenge involves the size of the resulting LNP when large, rigid cargo is encapsulated.

With respect to delivery of gene therapeutics to other types of cells, such as retinal cells, the optimal method to deliver these treatments to the retinal pigment epithelial (RPE) cells and/or photoreceptor cells remains to be improved to increase transduction efficacy and to reduce complications associated with the highly invasive surgery required for subretinal injection of viral vector suspensions. To date, when LNPs have been used for retinal gene transduction, the majority of the expression has been seen in the retinal pigmented epithelium (RPE) (Patel *et al.*, Journal of Controlled Release Volume 303, 10 June 2019, Pages 91-100) in the eyecup, and delivery of the gene therapy into the actual photoreceptors in the retina has remained a significant challenge.

Accordingly, to fully realize the potential of nucleic acid therapeutics to liver hepatocytes, as well as other cell types, such as retinal cells, an efficient *in vivo* delivery system for nucleic acids is needed.

SUMMARY

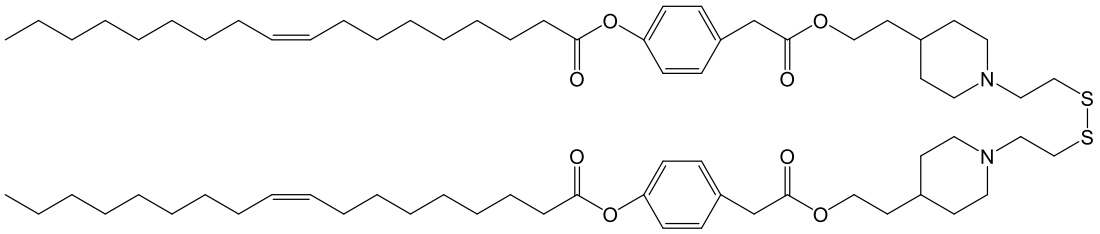
In a first aspect of the present disclosure, there is provided a pharmaceutical composition comprising a lipid nanoparticle (LNP) and a therapeutic nucleic acid (TNA), wherein the LNP comprises an apolipoprotein E (ApoE) polypeptide, or a fragment thereof, and/or an apolipoprotein B (ApoB) polypeptide, or a fragment thereof, linked to the LNP, and at least one pharmaceutically acceptable excipient, wherein the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are capable of binding a low-density lipoprotein (LDL) receptor, or an LDL receptor family member on a cell, and wherein the LNP is capable of being internalized into the cell.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a subject in need thereof.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a lipid nanoparticle (LNP), a therapeutic messenger RNA (mRNA), and at least one pharmaceutically acceptable excipient; wherein the LNP comprises:

an ApoE polypeptide or a fragment thereof, and/or an ApoB polypeptide or a fragment thereof, linked to the LNP; and

a cationic lipid having the structural formula:



(((((disulfanediylbis(ethane-2,1-diyl))bis(piperidine-1,4-diyl))bis(ethane-2,1-diyl))bis(oxy))bis(2-oxoethane-2,1-diyl))bis(4,1-phenylene) dioleate

(Lipid A),

wherein the LNP is capable of delivering the mRNA to a retinal cell.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a genetic disorder in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for:

delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA to the retina of a subject in need thereof; or

delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA to the liver of a subject in need thereof.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in therapy.

The present disclosure describes for the first time the combination of a lipid nanoparticle, such as a lipid nanoparticle having Lipid A as described herein as an ionizable or cationic lipid, with a gene therapy cargo, *e.g.*, an mRNA or a closed-ended DNA, for retinal delivery. Using mouse, rat, and non-human primate (NHP) *in vivo* systems, the present disclosure demonstrated that using LNP-delivered mRNA cargo, robust transgene expression can be achieved in the eye cup (RPE) and the neural retina, where the photoreceptors are. Importantly, the data presented herein showed that saturation was achieved at a low dose of LNP-delivered mRNA, thereby successfully achieving an excellent therapeutic index and tolerability of potential therapy Previously, when LNPs have been used for retinal gene transduction, the majority of the expression has been seen in the retinal pigmented epithelium (RPE) (Patel *et al.*, Journal of Controlled Release Volume 303, 10 June 2019, Pages 91-100) in the eyecup, while getting into the actual photoreceptors in the retina has remained a significant challenge. The results presented in the present disclosure surprisingly demonstrate not only that the LNPs are able to get into eye cup with expression equal to that of the RPE, but did so at a low dose.

In one example, the disclosure provides pharmaceutical composition comprising a lipid nanoparticle (LNP) and a therapeutic nucleic acid (TNA), wherein the LNP comprises an apolipoprotein E (ApoE) polypeptide, or a fragment thereof, and/or an apolipoprotein B (ApoB) polypeptide, or a fragment thereof, linked to the LNP, and at least one pharmaceutically acceptable excipient. According to some examples, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are capable of binding a low-density lipoprotein (LDL) receptor, or LDL receptor family member. According to further examples, the LNP

comprises an ApoE polypeptide, or a fragment thereof. According to some examples of any of the examples herein, the LNP comprises an ApoB polypeptide, or a fragment thereof. According to some examples of any of the examples herein, the ApoE polypeptide comprises an amino acid sequence of EELRVRLASHLRKLRKRLLRDADDLQKGGC (SEQ ID NO:1) or has a sequence similarity of at least 80% to the amino acid sequence set forth in SEQ ID NO:1. According to some examples, the ApoE polypeptide has a sequence similarity of at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% to the amino acid sequence set forth in SEQ ID NO:1. According to some examples, the ApoE polypeptide has a sequence similarity of at least 85% to the amino acid sequence set forth in SEQ ID NO:1. According to some examples, the ApoE polypeptide has a sequence similarity of at least 90% to the amino acid sequence set forth in SEQ ID NO:1. According to some examples, the ApoE polypeptide has a sequence similarity of at least 95% to the amino acid sequence set forth in SEQ ID NO:1. According to some examples, the ApoE polypeptide has a sequence similarity of at least 99% to the amino acid sequence set forth in SEQ ID NO:1. According to some examples, the ApoE polypeptide consists of SEQ ID NO:1. According to some examples of any of the examples herein, the ApoE polypeptide has a sequence similarity of at least 80% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide has a sequence similarity of at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide has a sequence similarity of at least 85% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide has a sequence similarity of at least 90% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide has a sequence similarity of at least 95% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide has a sequence similarity of at least 99% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide comprises SEQ ID NO:3. According to some examples, the ApoE polypeptide consists of SEQ ID NO:3. According to some examples of any of the examples herein, the ApoE polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGGC set forth in SEQ ID NO: 1, wherein the fragment is capable of binding to the LDL receptor. According to some examples of any of the examples herein, the ApoE polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGGC set forth in SEQ ID NO: 3, wherein the fragment is capable of binding to the LDL receptor. According to some examples, the LNP is internalized into the cell. According to some examples of any of the examples herein, the ApoB polypeptide comprises an amino acid sequence of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:2) or has a sequence similarity of at least 80% to SEQ ID NO:2. According to some examples, the ApoB

polypeptide has a sequence similarity of at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% to the amino acid sequence set forth in SEQ ID NO:2. According to some examples, the ApoB polypeptide has a sequence similarity of at least 85% to the amino acid sequence set forth in SEQ ID NO:2. According to some examples, the ApoB polypeptide has a sequence similarity of at least 90% to the amino acid sequence set forth in SEQ ID NO:2. According to some examples, the ApoB polypeptide has a sequence similarity of at least 95% to the amino acid sequence set forth in SEQ ID NO:2. According to some examples, the ApoB polypeptide has a sequence similarity of at least 99% to the amino acid sequence set forth in SEQ ID NO:2. According to some examples, the ApoB polypeptide has an amino acid sequence consisting of SEQ ID NO:2. According to some examples, the ApoB polypeptide consists of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:4). According to some examples of the examples herein, the ApoB polypeptide comprises an amino acid sequence of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:4) or has a sequence similarity of at least 80% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide has a sequence similarity of at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide has a sequence similarity of at least 85% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide has a sequence similarity of at least 90% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide has a sequence similarity of at least 95% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide has a sequence similarity of at least 99% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide consists of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:4). According to some examples of the examples herein, the ApoB polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGGC set forth in SEQ ID NO: 2, wherein the fragment is capable of binding to the LDL receptor. According to some examples of the examples herein, the ApoB polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGG set forth in SEQ ID NO:4 , wherein the fragment is capable of binding to the LDL receptor. According to some examples, the LNP is internalized into the cell. According to some examples of the examples herein, the LNP comprises a lipid selected from the group consisting of: a cationic lipid, a sterol or a derivative thereof, a non-cationic lipid, and at least one PEGylated lipid.

According to some examples of the examples herein, the TNA is encapsulated in the LNP. According to some examples of the examplesherein, the TNA is selected from the group consisting of minigenes, plasmids, minicircles, small interfering

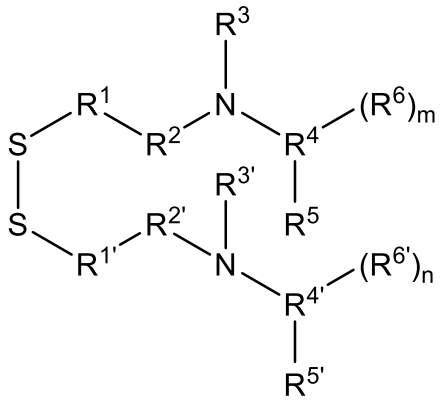
RNA (siRNA), microRNA (miRNA), antisense oligonucleotides (ASO), ribozymes, closed-ended (ceDNA), ministring, doggybone™, protelomere closed ended DNA, or dumbbell linear DNA, dicer-substrate dsRNA, small hairpin RNA (shRNA), asymmetrical interfering RNA (aiRNA), microRNA (miRNA), mRNA, tRNA, rRNA, gRNA, DNA viral vectors, viral RNA vector, non-viral vector and any combination thereof. According to some examples, the TNA is ceDNA. According to some examples, the ceDNA is linear duplex DNA. According to some examples, the TNA is mRNA. According to some examples, the TNA is siRNA. According to some examples, the TNA is a plasmid.

According to some examples of the examples herein, the LNP comprises a PEGylated lipid, wherein the PEGylated lipid is linked to the ApoE polypeptide, or the fragment thereof, or the PEGylated lipid is linked to the ApoB polypeptide, or the fragment thereof. According to some examples, the ApoE polypeptide, or the fragment thereof, or the ApoB polypeptide, or the fragment thereof, is chemically conjugated to the PEGylated lipid.

According to some examples of the examples herein, the pharmaceutical composition is administered to a subject. According to some examples, the subject is a human patient in need of treatment with LNP encapsulated with TNA.

According to some examples of the examples herein, the composition is delivered to a LDLR expressing tissue via binding of the ApoE polypeptide and/or the ApoB polypeptide present in the LNP to the LDLR receptor. According to some examples of the examples herein, the composition is delivered to retinal cells in the eye. According to some examples of the examples herein, the composition is delivered to a photoreceptor (PR) cell. According to some examples of the examples herein, the composition is delivered to a retinal pigment epithelium (RPE) cell. According to some examples of the examples herein, the composition is delivered to a photoreceptor (PR) cell and a retinal pigment epithelium (RPE) cell, wherein expression of the TNA in the PR cell and expression of the TNA in RPE cell is evenly distributed. According to some examples of the examples herein, the composition is delivered to hepatocytes in the liver. According to some examples of the examples herein, the composition is internalized in photoreceptor (PR) cell. According to some examples of the examples herein, the composition is internalized in a retinal pigment epithelium (RPE) cell. According to some examples of the examples herein, the composition is internalized in a hepatocyte.

According to some examples, the cationic lipid is represented by Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and $R^{1'}$ are each independently optionally substituted linear or branched C_{1-3} alkylene;

R^2 and $R^{2'}$ are each independently optionally substituted linear or branched C_{1-6} alkylene;

R^3 and $R^{3'}$ are each independently optionally substituted linear or branched C_{1-6} alkyl;

or alternatively, when R^2 is optionally substituted branched C_{1-6} alkylene, R^2 and R^3, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

or alternatively, when $R^{2'}$ is optionally substituted branched C_{1-6} alkylene, $R^{2'}$ and $R^{3'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^4 and $R^{4'}$ are each independently $–CR^a$, $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$;

R^a, for each occurrence, is independently H or C_{1-3} alkyl;

or alternatively, when R^4 is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, R^3 and R^4, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

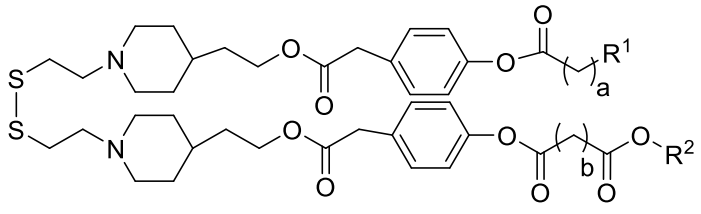
or alternatively, when $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^5 and $R^{5'}$ are each independently hydrogen, C_{1-20} alkylene or C_{2-20} alkenylene;

R^6 and $R^{6'}$, for each occurrence, are independently C_{1-20} alkylene, C_{3-20} cycloalkylene, or C_{2-20} alkenylene; and

m and n are each independently an integer selected from 1, 2, 3, 4, and 5.

According to some examples, the cationic lipid is represented by Formula (II):



(II);

or a pharmaceutically acceptable salt thereof, wherein:

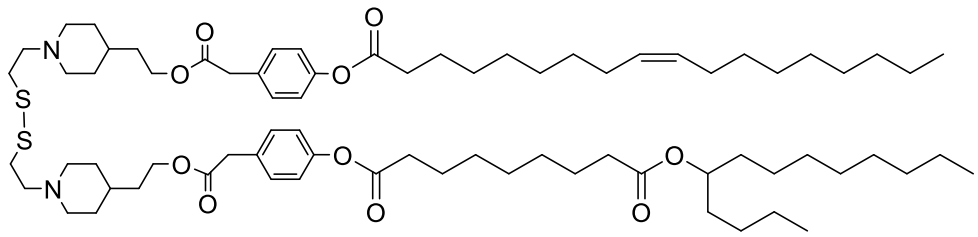
a is an integer ranging from 1 to 20;

b is an integer ranging from 2 to 10;

R^1 is absent or is selected from (C_2-C_{20})alkenyl, -C(O)O(C_2-C_{20})alkyl, and cyclopropyl substituted with (C_2-C_{20})alkyl; and

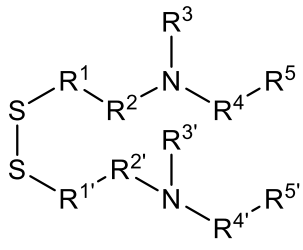
R^2 is (C_2-C_{20})alkyl.

According to some examples, the cationic lipid is 1-(4-(2-(2-(1-(2-((2-(4-(2-(2-(4-(oleoyloxy)phenyl)acetoxy)ethyl)piperidin-1-yl)ethyl)disulfaneyl)ethyl)piperidin-4-yl)ethoxy)-2-oxoethyl)phenyl) 9-(tridecan-5-yl) nonanedioate (Lipid 58), represented by the following structural formula:



Lipid 58

According to some examples, the lipid is represented by the Formula (V):



(V);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and $R^{1'}$ are each independently (C_1-C_6)alkylene optionally substituted with one or more groups selected from R^a;

R^2 and $R^{2'}$ are each independently (C_1-C_2)alkylene;

R^3 and $R^{3'}$ are each independently (C_1-C_6)alkyl optionally substituted with one or more groups selected from R^b;

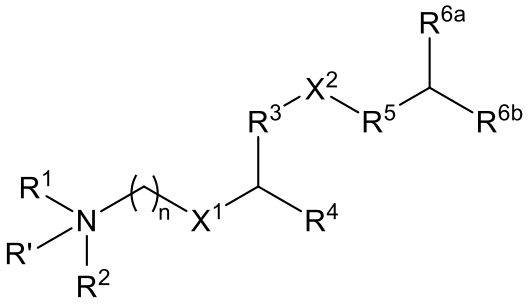
or alternatively, R^2 and R^3 and/or $R^{2'}$ and $R^{3'}$ are taken together with their intervening N atom to form a 4- to 7-membered heterocyclyl;

R^4 and $R^{4'}$ are each a (C_2-C_6)alkylene interrupted by –C(O)O-;

R^5 and $R^{5'}$ are each independently a (C_2-C_{30})alkyl or (C_2-C_{30})alkenyl, each of which are optionally interrupted with –C(O)O- or (C_3-C_6)cycloalkyl; and

R^a and R^b are each halo or cyano.

According to some examples, the cationic lipid is represented by Formula (XV):



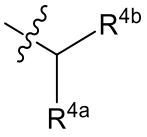
(XV)

or a pharmaceutically acceptable salt thereof, wherein:

R' is absent, hydrogen, or C_1-C_6 alkyl; provided that when R' is hydrogen or C_1-C_6 alkyl, the nitrogen atom to which R', R^1, and R^2 are all attached is protonated;

R^1 and R^2 are each independently hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

R^3 is C_1-C_{12} alkylene or C_2-C_{12} alkenylene;

R^4 is C_1-C_{16} unbranched alkyl, C_2-C_{16} unbranched alkenyl, or  ; wherein:

R^{4a} and R^{4b} are each independently C_1-C_{16} unbranched alkyl or C_2-C_{16} unbranched alkenyl;

R^5 is absent, C_1-C_8 alkylene, or C_2-C_8 alkenylene;

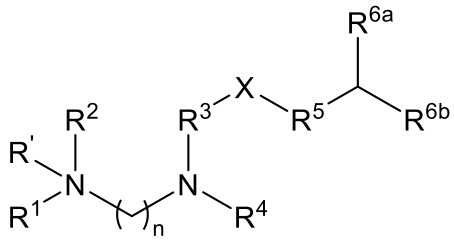
R^{6a} and R^{6b} are each independently C_7-C_{16} alkyl or C_7-C_{16} alkenyl; provided that the total number of carbon atoms in R^{6a} and R^{6b} as combined is greater than 15;

X^1 and X^2 are each independently -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C(R^a)=N-, -N=C(R^a)-, -C(R^a)=NO-, -O-N=C(R^a)-, -C(=O)NR^a-, -NR^aC(=O)-, -NR^aC(=O)NR^a-, -OC(=O)O-, -OSi(R^a)$_2$O-, -C(=O)(CR^a_2)C(=O)O-, or OC(=O)(CR^a_2)C(=O)-; wherein:

R^a, for each occurrence, is independently hydrogen or C_1-C_6 alkyl; and

n is an integer selected from 1, 2, 3, 4, 5, and 6.

According to some examples, the cationic lipid is represented by Formula (XX):



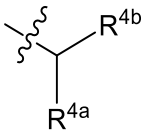
(XX)

or a pharmaceutically acceptable salt thereof, wherein:

R' is absent, hydrogen, or C_1-C_3 alkyl; provided that when R' is hydrogen or C_1-C_3 alkyl, the nitrogen atom to which R', R^1, and R^2 are all attached is protonated;

R^1 and R^2 are each independently hydrogen or C_1-C_3 alkyl;

R^3 is C_3-C_{10} alkylene or C_3-C_{10} alkenylene;

R^4 is C_1-C_{16} unbranched alkyl, C_2-C_{16} unbranched alkenyl, or  ; wherein:

R^{4a} and R^{4b} are each independently C_1-C_{16} unbranched alkyl or C_2-C_{16} unbranched alkenyl;

R^5 is absent, C_1-C_6 alkylene, or C_2-C_6 alkenylene;

R^{6a} and R^{6b} are each independently C_7-C_{14} alkyl or C_7-C_{14} alkenyl;

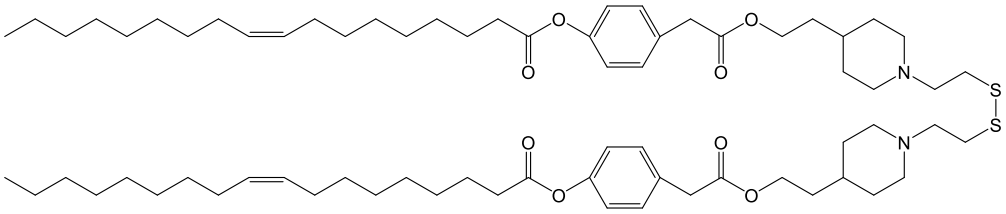
X is -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C(R^a)=N-, -N=C(R^a)-, -C(R^a)=NO-, -O-N=C(R^a)-, -C(=O)NR^a-, -NR^aC(=O)-, -NR^aC(=O)NR^a-, -OC(=O)O-, -OSi(R^a)$_2$O-, -C(=O)(CR^a_2)C(=O)O-, or OC(=O)(CR^a_2)C(=O)-; wherein:

R^a, for each occurrence, is independently hydrogen or C_1-C_6 alkyl; and

n is an integer selected from 1, 2, 3, 4, 5, and 6.

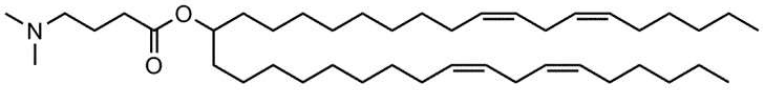
According to some examples, the cationic lipid is selected from any lipid in Table 2, Table 5, Table 6, Table 7, or Table 8.

According to some examples, the cationic lipid is Lipid A represented by the following structure:



or a pharmaceutically acceptable salt thereof.

According to some examples, the cationic lipid is MC3 (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA or MC3) having the following structure:



DLin-M-C3-DMA ("MC3")

or a pharmaceutically acceptable salt thereof.

According to some examples, the sterol or a derivative thereof is a cholesterol.

According to some examples, the sterol or a derivative thereof is beta-sitosterol.

According to some examples, the non-cationic lipid is selected from the group consisting of distearoyl-sn-glycero-phosphoethanolamine (DSPE), distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-

phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl-phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), monomethyl-phosphatidylethanolamine (such as 16-O-monomethyl PE), dimethyl-phosphatidylethanolamine (such as 16-O-dimethyl PE), 18-1-trans PE, 1-stearoyl-2-oleoyl-phosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucoylphosphatidylcholine (DEPC), palmitoyloleyolphosphatidylglycerol (POPG), dielaidoyl-phosphatidylethanolamine (DEPE), 1,2-dilauroyl-sn-glycero-3 -pho sphoethanolamine (DLPE); 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPHyPE); lecithin, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), cephalin, cardiolipin, phosphatidicacid,cerebrosides, dicetylphosphate, lysophosphatidylcholine, dilinoleoylphosphatidylcholine, and mixtures thereof. According to some examples, the non-cationic lipid is selected from the group consisting of dioleoylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC), and dioleoyl-phosphatidylethanolamine (DOPE).

According to some examples, the PEGylated lipid is selected from the group consisting of PEG-dilauryloxypropyl; PEG-dimyristyloxypropyl; PEG-dipalmityloxypropyl, PEG-distearyloxypropyl; l-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (DMG-PEG); 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[azido(polyethylene glycol], and distearoyl-rac-glycerol-poly(ethylene glycol) (DSG-PEG); PEG-dilaurylglycerol; PEG-dipalmitoylglycerol; PEG-disterylglycerol; PEG-dilaurylglycamide; PEG-dimyristylglycamide; PEG-dipalmitoylglycamide; PEG-disterylglycamide; (l-[8'-(Cholest-5-en-3[beta]-oxy)carboxamido-3',6'-dioxaoctanyl] carbamoyl-[omega]-methyl-poly(ethylene glycol) (PEG-cholesterol); 3,4-ditetradecoxylbenzyl-[omega]- methyl-poly(ethylene glycol) ether (PEG-DMB), and l,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N- [methoxy(polyethylene glycol) (DSPE-PEG), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-poly(ethylene glycol)-hydroxyl (DSPE-PEG-OH); and l,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N- [methoxy(polyethylene glycol)-azide (DSPE-PEG-azide). According to some examples, the PEGylated lipid is DMG-PEG, DSPE-PEG, DSPE-PEG-OH, DSPE-PEG-azide, DSG-PEG, or a combination thereof. According to some examples, the at least one PEGylated lipid is DMG-PEG2000, DSPE-PEG2000, DSPE-PEG2000-OH, DSPE-PEG2000-azide, DSG-PEG2000, or a combination thereof.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are

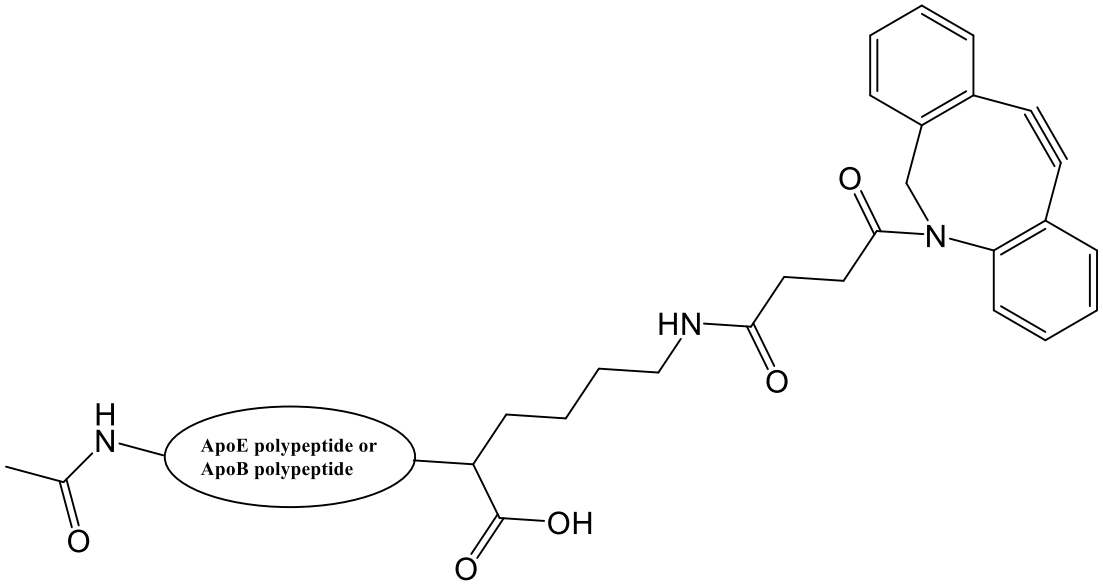
covalently linked to a PEGylated lipid of the LNP to form a PEGylated lipid conjugate. According to some examples, the PEGylated lipid to which the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked is DSPE-PEG or DSPE-PEG-azide.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a non-cleavable linker. According to some examples, the non-cleavable linker is a maleimide-containing linker.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a cleavable linker.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a pyridyldisulfide (PDS)-containing linker.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via strain promoted alkyne-azide cycloaddition (SPAAC) chemistry. According to some examples, the SPAAC chemistry comprises reaction between a cyclooctyne or a derivative thereof with an azide compound. According to some examples, the cyclooctyne or a derivative thereof is a dibenzocyclooctyne (DBCO) or a derivative thereof. According to some examples, the DBCO or a derivative thereof is a DBCO-functionalized ApoE polypeptide or a DBCO-functionalized ApoB polypeptide. According to some examples, the DBCO-functionalized ApoE polypeptide or wherein DBCO-functionalized ApoB polypeptide is represented by the following structure:



According to some examples of the examples herein, the azide compound is DSPE-PEG2000-azide or 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[azido(polyethylene glycol)-2000] or a salt thereof.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are linked to the LNP via one or more noncovalent interactions selected from hydrogen bonds, van der Waal bonds, ionic bonds, and hydrophobic bonds.

According to some examples of the examples herein, the cationic lipid is present at a molar percentage of about 30% to about 80%.

According to some examples of the examples herein, the sterol is present at a molar percentage of about 20% to about 50%.

According to some examples of the examples herein, the non-cationic lipid is present at a molar percentage of about 2% to about 20%.

According to some examples of the examples herein, the at least one PEGylated lipid is present at a molar percentage of about 2.1% to about 10% or wherein the at least one PEGylated lipid is present at a molar percentage of about 1% to about 2%.

According to some examples of the examples herein, the ApoE polypeptide and/or the ApoB polypeptide are present at a total amount of about 0.02 μg/μg of TNA to about 0.1 μg/μg of TNA.

According to some examples of the examples herein, the pharmaceutical composition further comprises dexamethasone palmitate.

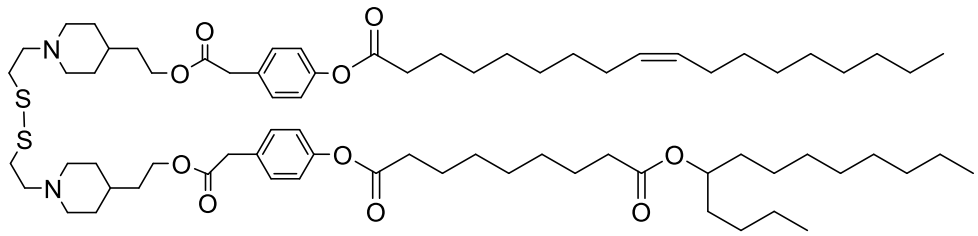
According to some examples of the examples herein,

the LNP comprises Lipid A, DOPC, cholesterol and DMG-PEG. According to some examples of the examples herein, the LNP comprises Lipid A, DOPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide. According to some examples of the examples herein, the LNP comprises Lipid A, DOPE, cholesterol and DMG-PEG. According to some examples of the examples herein, the LNP comprises Lipid A, DOPE, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide. According to some examples of the examples herein, the LNP comprises Lipid A, DSPC, cholesterol and DMG-PEG. According to some examples of the examples herein, the LNP comprises Lipid A, DSPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide. According to some examples of the examples herein, the LNP comprises Lipid A, DOPC, beta-sitosterol and DMG-PEG. According to some examples of the examples herein, the LNP comprises Lipid A, DOPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide. According to some examples of the examples herein, the LNP comprises Lipid A, DOPE, beta-sitosterol and DMG-PEG. According to some examples of the examples herein, the LNP comprises Lipid A, DOPE, beta-sitosterol, DMG-PEG, and DSPE-PEG

or DSPE-PEG-azide. According to some examples of the examples herein, the LNP comprises Lipid A, DSPC, beta-sitosterol and DMG-PEG. According to some examples of the examples herein, the LNP comprises Lipid A, DSPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide.

According to some examples of the examples herein, the DMG-PEG is DMG-PEG2000. According to some examples of the examples herein, the DSPE-PEG is DSPE-PEG2000 or DSPE-PEG5000. According to some examples of the examples herein, the e DSPE-PEG-azide is DSPE-PEG2000-azide or DSPE-PEG5000-azide. According to some examples, the LNP comprises Lipid A, DOPC, sterol, DMG-PEG and DSPE-PEG or DSPE-PEG-azide at molar ratios of about 51 : 7.3 : 38.3 : 2.9 : 0.5.

According to some examples of the examples herein, the LNP comprises 1-(4-(2-(2-(1-(2-((2-(4-(2-(2-(4-(oleoyloxy)phenyl)acetoxy)ethyl)piperidin-1-yl)ethyl)disulfaneyl)ethyl)piperidin-4-yl)ethoxy)-2-oxoethyl)phenyl) 9-(tridecan-5-yl) nonanedioate (Lipid 58), represented by the following structural formula:



Lipid 58

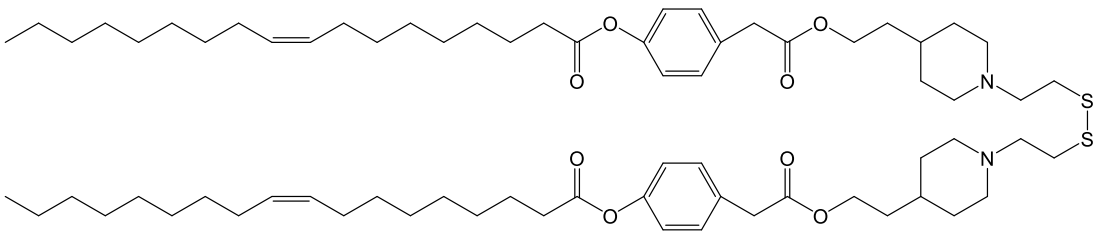
.

According to some examples of the examples herein, the LNP has a total lipid to TNA ratio of about 10:1 to about 40:1.

In another example, the disclosure provides a pharmaceutical composition comprising a lipid nanoparticle (LNP), a therapeutic messenger RNA (mRNA), and at least one pharmaceutically acceptable excipient; wherein the LNP comprises:

an ApoE polypeptide or a fragment thereof, and/or an ApoB polypeptide or a fragment thereof, linked to the LNP;

a cationic lipid having the structural formula:



(((((disulfanediylbis(ethane-2,1-diyl))bis(piperidine-1,4-diyl))bis(ethane-2,1-diyl))bis(oxy))bis(2-oxoethane-2,1-diyl))bis(4,1-phenylene) dioleate

(Lipid A)

and wherein the LNP is capable of delivering the mRNA to a retinal cell.

According to some examples, the LNP is capable of delivering the mRNA to a photoreceptor (PR) cell. According to some examples of the examples herein, the LNP is capable of delivering the mRNA to a retina pigment epithelium (RPE) cell. According to some examples of the examples herein, the LNP is capable of being internalized into the PR cell and/or the RPE cell. According to some examples of the examples herein, the e mRNA expression is evenly distributed in the PR cell and the RPE cell. According to some examples of the examples herein, the LNP is capable of delivering the mRNA to a retinal cell without resulting in retinal degradation or thinning of the outer nuclear layer (ONL). According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are capable of binding a low-density lipoprotein (LDL) receptor, or LDL receptor family member. According to some examples of the examples herein, the LNP comprises an ApoE polypeptide, or a fragment thereof. According to some examples of the examples herein, the LNP comprises an ApoB polypeptide, or a fragment thereof. According to some examples, the ApoE polypeptide comprises an amino acid sequence of EELRVRLASHLRKLRKRLLRDADDLQKGG (SEQ ID NO:3) or has a sequence similarity of at least 80% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide has a sequence similarity of at least 85%, at least 90%, at least 95%, or at least 99% to the amino acid sequence set forth in SEQ ID NO:3. According to some examples, the ApoE polypeptide consists of EELRVRLASHLRKLRKRLLRDADDLQKGG (SEQ ID NO:3). According to some examples of the examples herein, the ApoE polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGGC set forth in SEQ ID NO: 3, wherein the fragment is capable of binding to the LDL receptor. According to some examples, the ApoB polypeptide comprises an amino acid sequence of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:4) or has a sequence similarity of at least 80% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide has a sequence similarity of at least 85%, at least 90%, at least 95%, or at least 99% to the amino acid sequence set forth in SEQ ID NO:4. According to some examples, the ApoB polypeptide consists of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:4). According to some examples of the examples herein, the ApoB polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGG set forth in SEQ ID NO:4, wherein the fragment is capable of binding to the LDL receptor.

According to some examples of the examples herein, the mRNA is encapsulated in the LNP.

According to some examples of the examples herein, the LNP further comprises a lipid selected from the group consisting of a sterol or a derivative thereof, a non-cationic

lipid, and at least one PEGylated lipid. According to some examples, the sterol or a derivative thereof is a cholesterol. According to some examples, the sterol or a derivative thereof is beta-sitosterol.

According to some examples of the examples herein, the non-cationic lipid is selected from the group consisting of dioleoylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC), and dioleoyl-phosphatidylethanolamine (DOPE).

According to some examples of the examples herein, the PEGylated lipid is DMG-PEG, DSPE-PEG, DSPE-PEG-OH, DSPE-PEG-azide, DSG-PEG, or a combination thereof. According to some examples, the at least one PEGylated lipid is DMG-PEG2000, DSPE-PEG2000, DSPE-PEG2000-OH, DSPE-PEG-azide, DSG-PEG, or a combination thereof. According to some examples, the LNP comprises Lipid A, DOPC, cholesterol and DMG-PEG; or Lipid A, DOPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide; or Lipid A, DOPE, cholesterol and DMG-PEG; Lipid A, DOPE, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide; or Lipid A, DSPC, cholesterol and DMG-PEG; or Lipid A, DSPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide; Lipid A, DOPC, beta-sitosterol and DMG-PEG; or Lipid A, DOPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide; or Lipid A, DOPE, beta-sitosterol and DMG-PEG; or Lipid A, DOPE, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide; or Lipid A, DSPC, beta-sitosterol and DMG-PEG; or Lipid A, DSPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide. According to some examples, the DMG-PEG is DMG-PEG2000. According to some examples of the examples herein, the DSPE-PEG is DSPE-PEG2000 or DSPE-PEG5000. According to some examples of the examples herein, the DSPE-PEG-azide is DSPE-PEG2000-azide or DSPE-PEG5000-azide. According to some examples, the LNP comprises Lipid A, DOPC, sterol, DMG-PEG and DSPE-PEG or DSPE-PEG-azide at molar ratios of about 51 : 7.3 : 38.3 : 2.9 : 0.5.

According to some examples of the examples herein, the LNP comprises a PEGylated lipid, wherein the PEGylated lipid is linked to the ApoE polypeptide or the fragment thereof;or the PEGylated lipid is linked to the ApoB polypeptide, or the fragment thereof. According to some examples, the ApoE polypeptide or the fragment thereof, or the ApoB polypeptide or the fragment thereof is covalently linked to a PEGylated lipid of the LNP to form a PEGylated lipid conjugate. According to some examples, the PEGylated lipid to which the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked is DSPE-PEG or DSPE-PEG-azide.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a non-cleavable linker. According to some examples, the non-cleavable linker is a maleimide-containing linker.

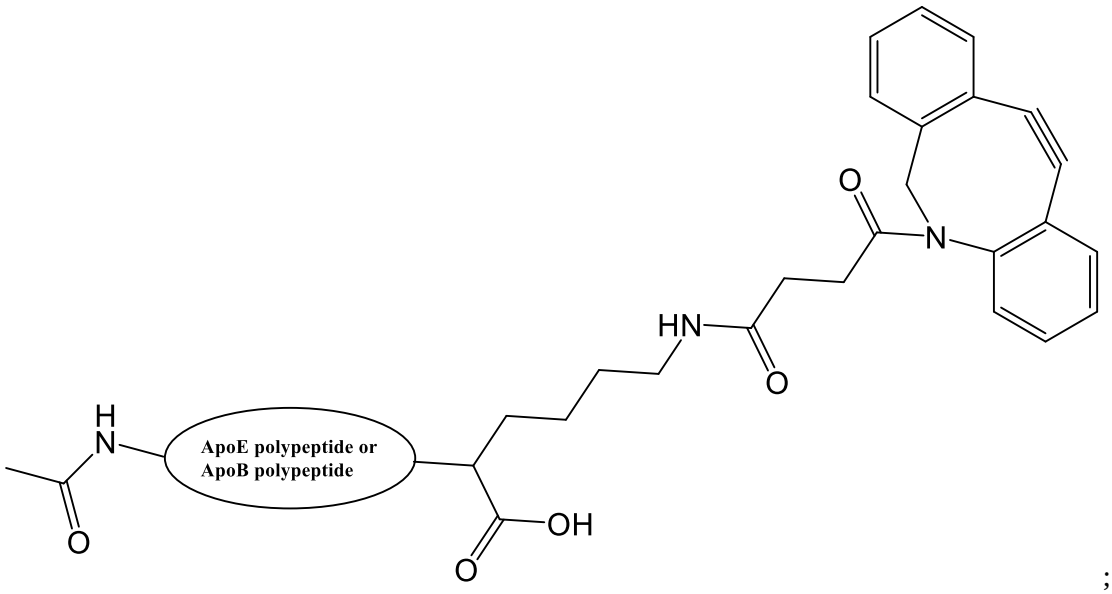
According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a cleavable linker.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a pyridyldisulfide (PDS)-containing linker.

According to some examples of the examples herein, the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via strain promoted alkyne-azide cycloaddition (SPAAC) chemistry.

According to some examples of the examples herein, the pharmaceutical composition is administered to a subject via subretinal injection, suprachoroidal injection, or intravitreal injection. According to some examples, the pharmaceutical composition is administered to a subject via subretinal injection.

According to another example, the disclosure provides a dibenzocyclooctyne (DBCO)-functionalized ApoE polypeptide or ApoB polypeptide represented by the following structure:



;

wherein:

ApoE polypeptide comprises an amino acid sequence of EELRVRLASHLRKLRKRLLRDADDLQKGG (SEQ ID NO:3) or has a sequence similarity of at least 80% to the amino acid sequence set forth in SEQ ID NO:3; and

the ApoB polypeptide comprises an amino acid sequence of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:4) or has a sequence similarity of at least 80% to the amino acid sequence set forth in SEQ ID NO:4.

According to some examples, the pharmaceutical composition is prepared using the DBCO-functionalized ApoE polypeptide or ApoB polypeptide as a reagent in combination with an azide compound.

According to other examples, the disclosure provides a lipid nanoparticle composition prepared using the DBCO-functionalized ApoE polypeptide or ApoB polypeptide of the examples herein, in combination with an azide compound. According to some examples, the azide compound is DSPE-PEG2000-azide or 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[azido(polyethylene glycol)-2000] or a salt thereof.

According to some examples of the examples herein, the LNP has a diameter ranging from about 40 nm to about 120 nm.

According to some examples of the examples herein, the nanoparticle has a diameter of less than about 100 nm.

According to some examples of the examples herein, the nanoparticle has a diameter of about 60 nm to about 80 nm.

According to another example, the disclosure provides a method of treating a genetic disorder in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition or the lipid composition of any one of the examples herein. According to some examples, the subject is a human. According to some examples of the method and its examples herein, the disorder is an ocular disorder. According to some examples of the method and its and examples herein, the the genetic disorder is selected from the group consisting of sickle-cell anemia, melanoma, hemophilia A (clotting factor VIII (FVIII) deficiency) and hemophilia B (clotting factor IX (FIX) deficiency), cystic fibrosis (CFTR), familial hypercholesterolemia (LDL receptor defect), hepatoblastoma, Wilson disease, phenylketonuria (PKU), congenital hepatic porphyria, inherited disorders of hepatic metabolism, Lesch Nyhan syndrome, sickle cell anemia, thalassaemias, xeroderma pigmentosum, Fanconi's anemia, retinitis pigmentosa, ataxia telangiectasia, Bloom's syndrome, retinoblastoma, mucopolysaccharide storage diseases (*e.g.*, Hurler syndrome (MPS Type I), Scheie syndrome (MPS Type I S), Hurler-Scheie syndrome (MPS Type I H-S), Hunter syndrome (MPS Type II), Sanfilippo Types A, B, C, and D (MPS Types III A, B, C, and D), Morquio Types A and B (MPS IVA and MPS IVB), Maroteaux-Lamy syndrome (MPS Type VI), Sly syndrome (MPS Type VII), hyaluronidase deficiency (MPS Type IX)), Niemann-Pick Disease Types A/B, C1 and C2, Fabry disease, Schindler disease, GM2-gangliosidosis Type II (Sandhoff Disease), Tay-Sachs disease, Metachromatic Leukodystrophy, Krabbe disease, Mucolipidosis Type I, II/III and IV, Sialidosis Types I and II, Glycogen Storage disease Types I and II (Pompe disease), Gaucher disease Types I, II and III, cystinosis, Batten disease, Aspartylglucosaminuria, Salla disease, Danon disease (LAMP-2 deficiency), Lysosomal Acid Lipase (LAL) deficiency, neuronal ceroid lipofuscinoses (CLN1-8, INCL, and LINCL), sphingolipidoses, galactosialidosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxia, spinal muscular atrophy, Friedreich's ataxia, Duchenne muscular dystrophy (DMD), Becker muscular dystrophies (BMD), dystrophic epidermolysis bullosa (DEB), ectonucleotide pyrophosphatase 1 deficiency, generalized arterial calcification of infancy

(GACI), Leber Congenital Amaurosis, Stargardt macular dystrophy (ABCA4), ornithine transcarbamylase (OTC) deficiency, Usher syndrome, age-related macular degeneration (AMD), alpha-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis (PFIC) type I (ATP8B1 deficiency), type II (ABCB11), type III (ABCB4), or type IV (TJP2), and Cathepsin A deficiency.

According to some examples, the genetic disorder is hemophilia A. According to some examples, the genetic disorder is hemophilia B. According to some examples, the genetic disorder is phenylketonuria (PKU). According to some examples, the genetic disorder is Wilson disease. According to some examples, the genetic disorder is Gaucher disease Types I, II and III. According to some examples, the genetic disorder is Stargardt macular dystrophy. According to some examples, the genetic disorder is LCA10. According to some examples, the genetic disorder is Usher syndrome. According to some examples, the genetic disorder is wet AMD.

According to another example, the disclosure provides a method of delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA to the retina of a subject, comprising administering to the subject an effective amount of the pharmaceutical composition or the lipid nanoparticle composition of any one of the examples herein.

According to another example, the disclosure provides a method of delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA to the liver of a subject, comprising administering to the subject an effective amount of the pharmaceutical composition or the lipid nanoparticle composition of any one of the examples herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the present disclosure, briefly summarized above and discussed in greater detail below, can be understood by reference to the illustrative embodiments of the disclosure depicted in the appended drawings. However, the appended drawings illustrate only typical embodiments of the disclosure and are therefore not to be considered limiting of scope, for the disclosure may admit to other equally effective embodiments.

FIG. 1A-FIG. 1D present graphs that show LNP-delivered mRNA and LNP-delivered ceDNA were tolerated in both mouse (bottom panels, **FIG. 1B** and **FIG. 1D**) and rat (top panels, **FIG. 1A** and **FIG. 1C**). Degeneration score is shown at Day 21.

FIG. 2A – FIG. 2I show the results of fundus imaging for GFP expression in rats and mice at 24 hours, as described in Example 2. **FIGS. 2A-2I** show fundus imaging of Lipid A LNP/GFP mRNA treated mice (0.4 µg) (Group 2 as described in Table 9, **FIGS. 2A-2E**) compared to non-treated control mice (Group 1 as described in Table 9, **FIGS. 2F-2I**).

FIG. 3 is a graph that shows the amount of GFP in the neural retina and RPE/eye cup as determined by ELISA after dosing of wild type mice with Lipid A LNP/GFP mRNA (0.4 µg) (Group 2 as described in Table 9) at 12 hours and 24 hours post-treatment.

CLAIMS

What is Claimed is:

1. A pharmaceutical composition comprising a lipid nanoparticle (LNP) and a therapeutic nucleic acid (TNA), wherein the LNP comprises an apolipoprotein E (ApoE) polypeptide, or a fragment thereof, and/or an apolipoprotein B (ApoB) polypeptide, or a fragment thereof, linked to the LNP, and at least one pharmaceutically acceptable excipient, wherein the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are capable of binding a low-density lipoprotein (LDL) receptor, or an LDL receptor family member on a cell, and wherein the LNP is capable of being internalized into the cell.

2. The pharmaceutical composition of claim 1, wherein the ApoE polypeptide linked to the LNP comprises:

an amino acid sequence set forth in EELRVRLASHLRKLRKRLLRDADDLQKGGC (SEQ ID NO:1) or an amino acid sequence having at least 85% similarity to the amino acid sequence set forth in SEQ ID NO:1; or

an amino acid sequence set forth in EELRVRLASHLRKLRKRLLRDADDLQKGG (SEQ ID NO:3) or an amino acid sequence having at least 85% similarity to the amino acid sequence set forth in SEQ ID NO:3.

3. The pharmaceutical composition of claim 2, wherein the ApoE polypeptide linked to the LNP consists of SEQ ID NO:1 or SEQ ID NO: 3.

4. The pharmaceutical composition of claim 1, wherein the ApoE polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGGC (SEQ ID NO: 1), wherein the fragment is capable of binding to the LDL receptor.

5. The pharmaceutical composition of claim 1, wherein the ApoE polypeptide linked to the LNP is a fragment of EELRVRLASHLRKLRKRLLRDADDLQKGGC (SEQ ID NO: 3), wherein the fragment is capable of binding to the LDL receptor.

6. The pharmaceutical composition of claim 1, wherein the ApoB polypeptide linked to the LNP comprises:

an amino acid sequence set forth in SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:2), or an amino acid sequence having at least 85% sequence similarity to SEQ ID NO:2; or

an amino acid sequence set forth in SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGG (SEQ ID NO:4) or an amino acid sequence having at least 85% similarity to the amino acid sequence set forth in SEQ ID NO:4.

7. The pharmaceutical composition of claim 6, wherein the ApoB polypeptide linked to the LNP consists of SEQ ID NO: 2 or SEQ ID NO: 4.

8. The pharmaceutical composition of claim 1, wherein the ApoB polypeptide linked to the LNP is a fragment of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO: 2), wherein the fragment is capable of binding to the LDL receptor.

9. The pharmaceutical composition of claim 1, wherein the ApoB polypeptide linked to the LNP is a fragment of SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGG (SEQ ID NO: 4), wherein the fragment is capable of binding to the LDL receptor.

10. The pharmaceutical composition of any one of claims 1 to 9, wherein:

the LNP comprises a lipid selected from the group consisting of: a cationic lipid, a sterol or a derivative thereof, a non-cationic lipid, and at least one PEGylated lipid; and/or

the TNA is selected from the group consisting of: a minigene, a plasmid, a minicircle, a small interfering RNA (siRNA), a microRNA (miRNA), an antisense oligonucleotide (ASO), a ribozyme, a closed-ended DNA (ceDNA), a ministering DNA, a doggybone™ DNA, a protelomere closed ended DNA, a dumbbell linear DNA, a linear duplex DNA, a dicer-substrate dsRNA, a small hairpin RNA (shRNA), an asymmetrical interfering RNA (aiRNA), a microRNA (miRNA), an mRNA, a tRNA, an rRNA, a gRNA, a DNA viral vector, a viral RNA vector, a non-viral vector, and any combination thereof.

11. The pharmaceutical composition of any one of claims 1 to 10, wherein the TNA is encapsulated in the LNP.

12. The pharmaceutical composition of any one of claims 1-11, wherein:

the LNP comprises at least one PEGylated lipid, wherein the at least one PEGylated lipid is linked to the ApoE polypeptide, or the fragment thereof;

the LNP comprises at least one PEGylated lipid, wherein the at least one PEGylated lipid is linked to the ApoB polypeptide, or the fragment thereof;

the LNP comprises at least one PEGylated lipid, wherein the ApoE polypeptide, or the fragment thereof, or the ApoB polypeptide, or the fragment thereof, is chemically conjugated to the at least one PEGylated lipid;

the LNP comprises a cationic lipid selected from the group consisting of: a lipid set forth in Table 2, Table 5, Table 6, Table 7, and Table 8;

the LNP comprises a non-cationic lipid selected from the group consisting of: distearoyl-sn-glycero-phosphoethanolamine (DSPE), distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl-phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), monomethyl-phosphatidylethanolamine (such as 16-O-monomethyl PE), dimethyl-phosphatidylethanolamine (such as 16-O-dimethyl PE), 18-1-trans PE, 1-stearoyl-2-oleoyl-phosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucoylphosphatidylcholine (DEPC), palmitoyloleyolphosphatidylglycerol (POPG), dielaidoyl-phosphatidylethanolamine (DEPE), 1,2-dilauroyl-sn-glycero-3 -pho sphoethanolamine (DLPE); 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPHyPE); lecithin, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), cephalin, cardiolipin, phosphatidicacid,cerebrosides, dicetylphosphate, lysophosphatidylcholine, dilinoleoylphosphatidylcholine, and mixtures thereof;

the LNP comprises a sterol or a derivative thereof, wherein the sterol or a derivative thereof is a cholesterol; and/or

the LNP comprises a sterol or a derivative thereof, wherein the sterol or a derivative thereof is beta-sitosterol.

13. Use of a pharmaceutical composition of any one of claims 1-12, in the manufacture of a medicament for treating a subject in need thereof.

14. The use of claim 13, wherein:

the subject is a human patient in need of treatment with a TNA;

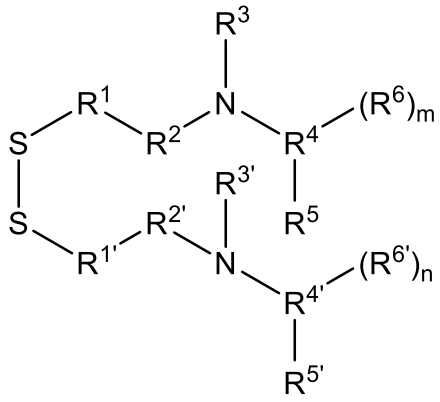
the pharmaceutical composition is to be delivered to a LDLR expressing tissue via binding of the ApoE polypeptide and/or the ApoB polypeptide present in the LNP to the LDLR receptor;

the pharmaceutical composition is to be delivered to a cell selected from the group consisting of: a retinal cell in the eye, a photoreceptor (PR) cell, a retinal pigment epithelium (RPE) cell, and a hepatocyte in the liver; and/or

the pharmaceutical composition is to be delivered to a photoreceptor (PR) cell and a retinal pigment epithelium (RPE) cell, wherein expression of the TNA in the PR cell and expression of the TNA in the RPE cell is evenly distributed.

15. The pharmaceutical composition of claim 10, wherein the cationic lipid is represented by:

(i) Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and $R^{1'}$ are each independently optionally substituted linear or branched C_{1-3} alkylene;

R^2 and $R^{2'}$ are each independently optionally substituted linear or branched C_{1-6} alkylene;

R^3 and $R^{3'}$ are each independently optionally substituted linear or branched C_{1-6} alkyl;

or alternatively, when R^2 is optionally substituted branched C_{1-6} alkylene, R^2 and R^3, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

or alternatively, when $R^{2'}$ is optionally substituted branched C_{1-6} alkylene, $R^{2'}$ and $R^{3'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^4 and $R^{4'}$ are each independently $–CR^a$, $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$;

R^a, for each occurrence, is independently H or C_{1-3} alkyl;

or alternatively, when R^4 is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, R^3 and R^4, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

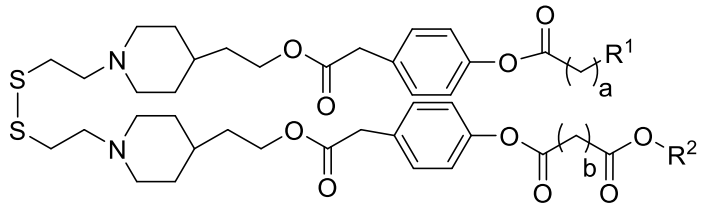
or alternatively, when $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^5 and $R^{5'}$ are each independently hydrogen, C_{1-20} alkylene or C_{2-20} alkenylene;

R^6 and $R^{6'}$, for each occurrence, are independently C_{1-20} alkylene, C_{3-20} cycloalkylene, or C_{2-20} alkenylene; and

m and n are each independently an integer selected from 1, 2, 3, 4, and 5;

(ii) Formula (II):



(II);

or a pharmaceutically acceptable salt thereof, wherein:

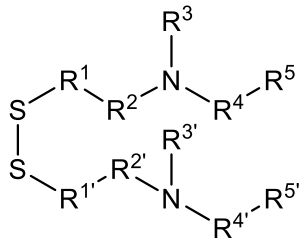
a is an integer ranging from 1 to 20;

b is an integer ranging from 2 to 10;

R^1 is absent or is selected from (C_2-C_{20})alkenyl, -C(O)O(C_2-C_{20})alkyl, and cyclopropyl substituted with (C_2-C_{20})alkyl; and

R^2 is (C_2-C_{20})alkyl;

(iii) Formula (V):



(V);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and $R^{1'}$ are each independently (C_1-C_6)alkylene optionally substituted with one or more groups selected from R^a;

R^2 and $R^{2'}$ are each independently (C_1-C_2)alkylene;

R^3 and $R^{3'}$ are each independently (C_1-C_6)alkyl optionally substituted with one or more groups selected from R^b;

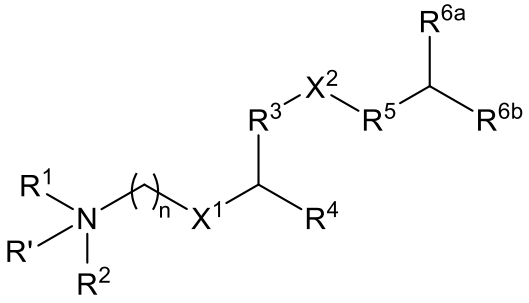
or alternatively, R^2 and R^3 and/or $R^{2'}$ and $R^{3'}$ are taken together with their intervening N atom to form a 4- to 7-membered heterocyclyl;

R^4 and $R^{4'}$ are each a (C_2-C_6)alkylene interrupted by –C(O)O-;

R^5 and $R^{5'}$ are each independently a (C_2-C_{30})alkyl or (C_2-C_{30})alkenyl, each of which are optionally interrupted with –C(O)O- or (C_3-C_6)cycloalkyl; and

R^a and R^b are each halo or cyano;

(iv) Formula (XV):



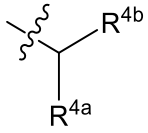
(XV)

or a pharmaceutically acceptable salt thereof, wherein:

R' is absent, hydrogen, or C_1-C_6 alkyl; provided that when R' is hydrogen or C_1-C_6 alkyl, the nitrogen atom to which R', R^1, and R^2 are all attached is protonated;

R^1 and R^2 are each independently hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

R^3 is C_1-C_{12} alkylene or C_2-C_{12} alkenylene;

R^4 is C_1-C_{16} unbranched alkyl, C_2-C_{16} unbranched alkenyl, or  ; wherein:

R^{4a} and R^{4b} are each independently C_1-C_{16} unbranched alkyl or C_2-C_{16} unbranched alkenyl;

R^5 is absent, C_1-C_8 alkylene, or C_2-C_8 alkenylene;

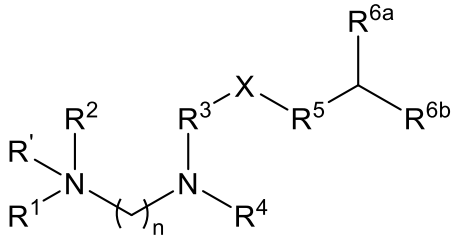
R^{6a} and R^{6b} are each independently C_7-C_{16} alkyl or C_7-C_{16} alkenyl; provided that the total number of carbon atoms in R^{6a} and R^{6b} as combined is greater than 15;

X^1 and X^2 are each independently -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C(R^a)=N-, -N=C(R^a)-, -C(R^a)=NO-, -O-N=C(R^a)-, -C(=O)NR^a-, -NR^aC(=O)-, -NR^aC(=O)NR^a-, -OC(=O)O-, -OSi(R^a)$_2$O-, -C(=O)(CR^a_2)C(=O)O-, or OC(=O)(CR^a_2)C(=O)-; wherein:

R^a, for each occurrence, is independently hydrogen or C_1-C_6 alkyl; and

n is an integer selected from 1, 2, 3, 4, 5, and 6; or

(v) Formula (XX):



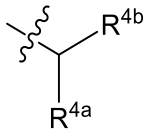
(XX)

or a pharmaceutically acceptable salt thereof, wherein:

R’ is absent, hydrogen, or C_1-C_3 alkyl; provided that when R’ is hydrogen or C_1-C_3 alkyl, the nitrogen atom to which R’, R^1, and R^2 are all attached is protonated;

R^1 and R^2 are each independently hydrogen or C_1-C_3 alkyl;

R^3 is C_3-C_{10} alkylene or C_3-C_{10} alkenylene;

R^4 is C_1-C_{16} unbranched alkyl, C_2-C_{16} unbranched alkenyl, or  ; wherein:

R^{4a} and R^{4b} are each independently C_1-C_{16} unbranched alkyl or C_2-C_{16} unbranched alkenyl;

R^5 is absent, C_1-C_6 alkylene, or C_2-C_6 alkenylene;

R^{6a} and R^{6b} are each independently C_7-C_{14} alkyl or C_7-C_{14} alkenyl;

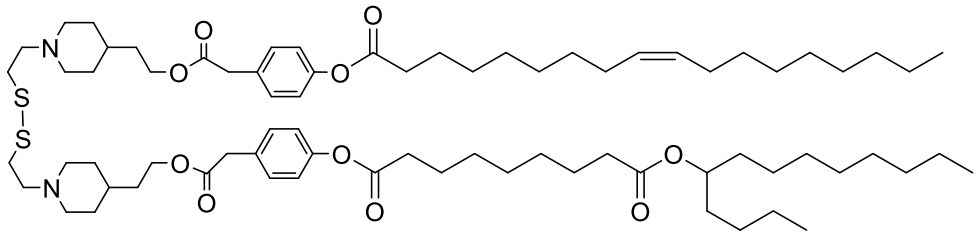
X is -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C(R^a)=N-, -N=C(R^a)-, -C(R^a)=NO-, -O-N=C(R^a)-, -C(=O)NR^a-, -NR^aC(=O)-, -NR^aC(=O)NR^a-, -OC(=O)O-, -OSi(R^a)$_2$O-, -C(=O)(CR^a_2)C(=O)O-, or OC(=O)(CR^a_2)C(=O)-; wherein:

R^a, for each occurrence, is independently hydrogen or C_1-C_6 alkyl; and

n is an integer selected from 1, 2, 3, 4, 5, and 6.

16. The pharmaceutical composition of claim 10, wherein:

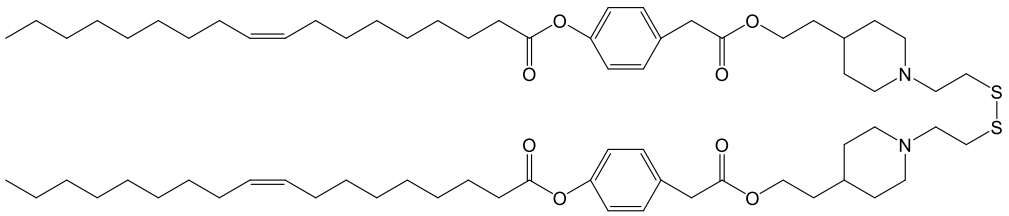
(i) the cationic lipid is 1-(4-(2-(2-(1-(2-((2-(4-(2-(2-(4-(oleoyloxy)phenyl)acetoxy)ethyl)piperidin-1-yl)ethyl)disulfaneyl)ethyl)piperidin-4-yl)ethoxy)-2-oxoethyl)phenyl) 9-(tridecan-5-yl) nonanedioate (Lipid 58), represented by the following structural formula:



Lipid 58

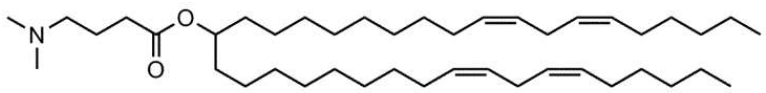
;

(ii) the cationic lipid is Lipid A represented by the following structure:



or a pharmaceutically acceptable salt thereof; or

(iii) the cationic lipid is MC3 (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA or MC3) having the following structure:



DLin-M-C3-DMA ("MC3")

or a pharmaceutically acceptable salt thereof.

17. The pharmaceutical composition of claim 12, wherein:

the at least one PEGylated lipid is selected from the group consisting of: PEG-dilauryloxypropyl; PEG-dimyristyloxypropyl; PEG-dipalmityloxypropyl, PEG-distearyloxypropyl; l-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (DMG-PEG); 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[azido(polyethylene glycol], and distearoyl-rac-glycerol-poly(ethylene glycol) (DSG-PEG); PEG-dilaurylglycerol; PEG-dipalmitoylglycerol; PEG-disterylglycerol; PEG-dilaurylglycamide; PEG-dimyristylglycamide; PEG-dipalmitoylglycamide; PEG-disterylglycamide; (l-[8'-(Cholest-5-en-3[beta]-oxy)carboxamido-3',6'-dioxaoctanyl] carbamoyl-[omega]-methyl-poly(ethylene glycol) (PEG-cholesterol); 3,4-ditetradecoxylbenzyl-[omega]- methyl-poly(ethylene glycol) ether (PEG-DMB), and l,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol) (DSPE-PEG), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-poly(ethylene glycol)-hydroxyl (DSPE-PEG-OH); and l,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N- [methoxy(polyethylene glycol)-azide (DSPE-PEG-azide);

the at least one PEGylated lipid is selected from the group consisting of: DMG-PEG2000, DSPE-PEG2000, DSPE-PEG2000-OH, DSPE-PEG2000-azide, DSG-PEG2000, and a combination thereof;

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the at least one PEGylated lipid of the LNP to form a PEGylated lipid conjugate; and/or

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the at least one PEGylated lipid comprising DSPE-PEG or DSPE-PEG-azide.

18. The pharmaceutical composition of any one of claims 1-12, wherein:

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a non-cleavable linker;

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a non-cleavable maleimide-containing linker;

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a cleavable linker;

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a pyridyldisulfide (PDS)-containing linker;

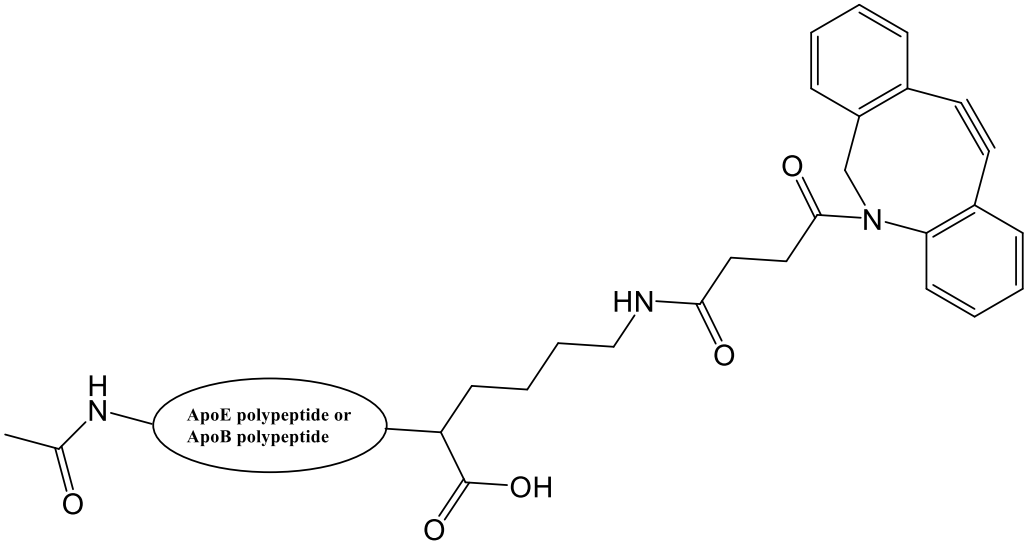
the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via strain promoted alkyne-azide cycloaddition (SPAAC) chemistry; and/or

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are linked to the LNP via one or more noncovalent interactions selected from hydrogen bonds, van der Waal bonds, ionic bonds, and hydrophobic bonds.

19. The pharmaceutical composition of claim 18, wherein the SPAAC chemistry comprises reaction between a cyclooctyne or a derivative thereof with an azide compound, wherein:

the cyclooctyne or a derivative thereof is a dibenzocyclooctyne (DBCO) or a derivative thereof, wherein:

the DBCO or a derivative thereof is a DBCO-functionalized ApoE polypeptide or a DBCO-functionalized ApoB polypeptide represented by the following structure:



;and/or

the azide compound is DSPE-PEG2000-azide or 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[azido(polyethylene glycol)-2000] or a salt thereof.

20. The pharmaceutical composition of any one of claims 15 to 16, wherein:

the cationic lipid is present at a molar percentage of about 30% to about 80%;

the sterol is present at a molar percentage of about 20% to about 50%;

the non-cationic lipid is present at a molar percentage of about 2% to about 20%;

the PEGylated lipid is present at a molar percentage of about 2.1% to about 10%; or
the PEGylated lipid is present at a molar percentage of about 1% to about 2%.

21. The pharmaceutical composition of any one of claims 1-12 or 15-20, wherein:
the ApoE polypeptide and/or the ApoB polypeptide are present at a total amount of about 0.02 µg/µg of TNA to about 0.1 µg/µg of TNA.

22. The pharmaceutical composition of any one of claims 1-12 or 15-21, further comprising dexamethasone palmitate.

23. The pharmaceutical composition of claim 16, wherein the LNP comprises:
Lipid A, DOPC, cholesterol and DMG-PEG;
Lipid A, DOPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide.
Lipid A, DOPE, cholesterol and DMG-PEG;
Lipid A, DOPE, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;
Lipid A, DSPC, cholesterol and DMG-PEG;
Lipid A, DSPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;
Lipid A, DOPC, beta-sitosterol and DMG-PEG
Lipid A, DOPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;
Lipid A, DOPE, beta-sitosterol and DMG-PEG;
Lipid A, DOPE, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;
Lipid A, DSPC, beta-sitosterol and DMG-PEG; or
Lipid A, DSPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide.

24. The pharmaceutical composition of claim 23, wherein:
the DMG-PEG is DMG-PEG2000;
the DSPE-PEG is DSPE-PEG2000 or DSPE-PEG5000; or
the DSPE-PEG-azide is DSPE-PEG2000-azide or DSPE-PEG5000-azide.

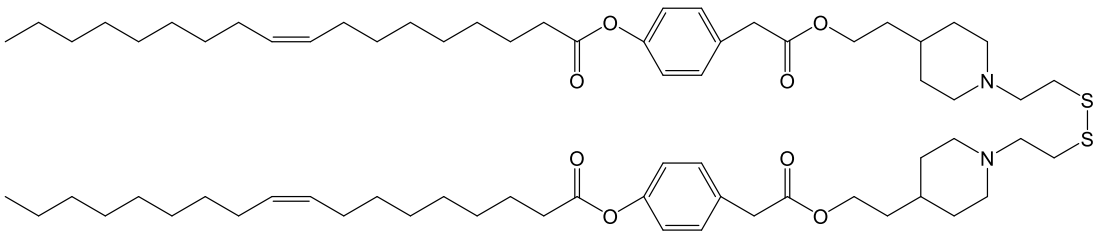
25. The pharmaceutical composition of claim 23, wherein the LNP comprises Lipid A, DOPC, sterol, DMG-PEG and DSPE-PEG or DSPE-PEG-azide at molar ratios of about 51 : 7.3 : 38.3 : 2.9 : 0.5.

26. The pharmaceutical composition of any one of claims 1-12 or 15-25, wherein the LNP has a total lipid to TNA ratio of about 10:1 to about 40:1.

27. A pharmaceutical composition comprising a lipid nanoparticle (LNP), a therapeutic messenger RNA (mRNA), and at least one pharmaceutically acceptable excipient; wherein the LNP comprises:

an ApoE polypeptide or a fragment thereof, and/or an ApoB polypeptide or a fragment thereof, linked to the LNP; and

a cationic lipid having the structural formula:



(((((disulfanediylbis(ethane-2,1-diyl))bis(piperidine-1,4-diyl))bis(ethane-2,1-diyl))bis(oxy))bis(2-oxoethane-2,1-diyl))bis(4,1-phenylene) dioleate

(Lipid A),

wherein the LNP is capable of delivering the mRNA to a retinal cell.

28. The pharmaceutical composition of claim 27, wherein:

the LNP is capable of delivering the mRNA to a photoreceptor (PR) cell;

the LNP is capable of delivering the mRNA to a retina pigment epithelium (RPE) cell;

the LNP is capable of being internalized into a PR cell and/or an RPE cell, wherein the mRNA expression is evenly distributed in the PR cell and the RPE cell;

the LNP is capable of delivering the mRNA to a retinal cell without resulting in retinal degradation or thinning of the outer nuclear layer (ONL); and/or

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are capable of binding a low-density lipoprotein (LDL) receptor, or LDL receptor family member.

29. The pharmaceutical composition of any one of claims 27 or 28, wherein the LNP comprises an ApoE polypeptide, or a fragment thereof, comprising:

an amino acid sequence set forth in EELRVRLASHLRKLRKRLLRDADDLQKGGC (SEQ ID NO:1) or an amino acid sequence having at least 85% similarity to the amino acid sequence set forth in SEQ ID NO:1; or

an amino acid sequence set forth in EELRVRLASHLRKLRKRLLRDADDLQKGG (SEQ ID NO:3) or an amino acid sequence having at least 85% similarity to the amino acid sequence set forth in SEQ ID NO:3.

30. The pharmaceutical composition of any one of claims 27 or 28, wherein the LNP comprises an ApoB polypeptide, or a fragment thereof, comprising:

an amino acid sequence set forth in SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:2), or an amino acid sequence having at least 85% sequence similarity to SEQ ID NO:2; or

an amino acid sequence set forth in SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGG (SEQ ID NO:4) or an amino acid sequence having at least 85% similarity to the amino acid sequence set forth in SEQ ID NO:4.

31. The pharmaceutical composition of any one of claims 27 to 30, wherein the mRNA is encapsulated in the LNP.

32. The pharmaceutical composition of any one of claims 27 to 31, wherein the LNP further comprises a lipid selected from the group consisting of a sterol or a derivative thereof, a non-cationic lipid, and at least one PEGylated lipid.

33. The pharmaceutical composition of claim 32, wherein:

the sterol or a derivative thereof is a cholesterol;

the sterol or a derivative thereof is beta-sitosterol;

the non-cationic lipid is selected from the group consisting of: dioleoylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC), and dioleoyl-phosphatidylethanolamine (DOPE); and/or

the at least one PEGylated lipid is selected from the group consisting of: DMG-PEG, DSPE-PEG, DSPE-PEG-OH, DSPE-PEG-azide, DSG-PEG, DMG-PEG2000, DSPE-PEG2000, DSPE-PEG2000-OH, DSPE-PEG-azide, and a combination thereof.

34. The pharmaceutical composition of claim 27, wherein the LNP comprises:

Lipid A, DOPC, cholesterol and DMG-PEG;

Lipid A, DOPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;

Lipid A, DOPE, cholesterol and DMG-PEG;

Lipid A, DOPE, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;

Lipid A, DSPC, cholesterol and DMG-PEG;

Lipid A, DSPC, cholesterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;

Lipid A, DOPC, beta-sitosterol and DMG-PEG;

Lipid A, DOPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;

Lipid A, DOPE, beta-sitosterol and DMG-PEG;

Lipid A, DOPE, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide;

Lipid A, DSPC, beta-sitosterol and DMG-PEG; or

Lipid A, DSPC, beta-sitosterol, DMG-PEG, and DSPE-PEG or DSPE-PEG-azide.

35. The pharmaceutical composition of claim 34, wherein:

the DMG-PEG is DMG-PEG2000;

the DSPE-PEG is DSPE-PEG2000 or DSPE-PEG5000.

the DSPE-PEG-azide is DSPE-PEG2000-azide or DSPE-PEG5000-azide; and/or

the LNP comprises Lipid A, DOPC, sterol, DMG-PEG and DSPE-PEG or DSPE-PEG-azide at molar ratios of about 51 : 7.3 : 38.3 : 2.9 : 0.5.

36. The pharmaceutical composition of any one of claims 27 to 35, wherein the LNP comprises at least one PEGylated lipid, wherein:

the at least one PEGylated lipid is linked to the ApoE polypeptide or the fragment thereof;

the at least one PEGylated lipid is linked to the ApoB polypeptide, or the fragment thereof;

the ApoE polypeptide or the fragment thereof, or the ApoB polypeptide or the fragment thereof is covalently linked to the at least one PEGylated lipid of the LNP to form a PEGylated lipid conjugate; and/or

the at least one PEGylated lipid is DSPE-PEG or DSPE-PEG-azide, which is covalently linked to the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof.

37. The pharmaceutical composition of any one of claims 27 to 36, wherein:

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a non-cleavable linker;

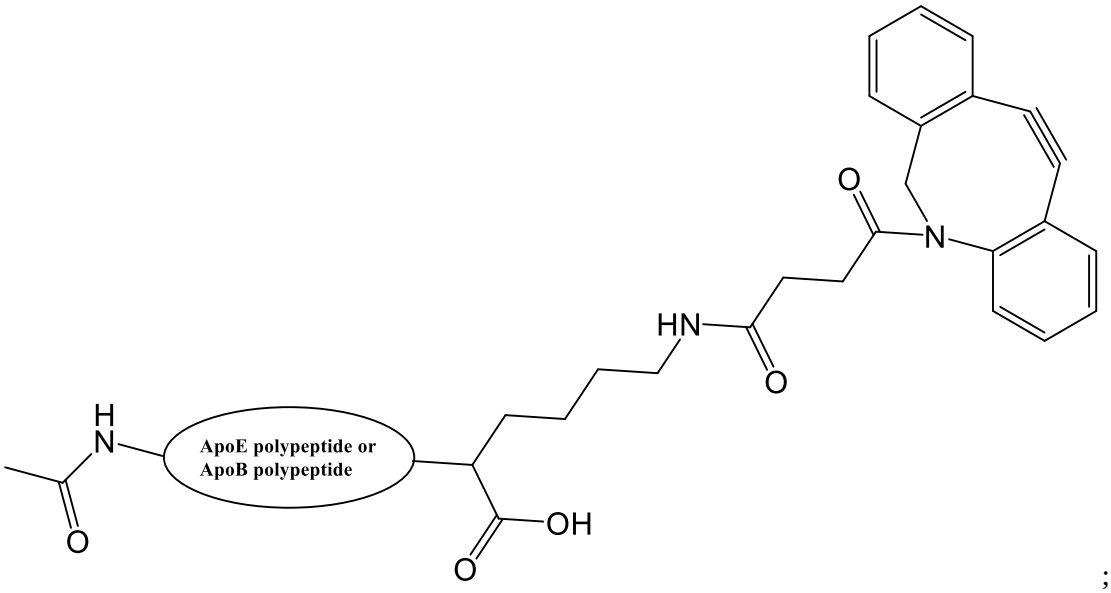
the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a maleimide-containing linker;

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a cleavable linker;

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via a pyridyldisulfide (PDS)-containing linker; and/or

the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, are covalently linked to the LNP via strain promoted alkyne-azide cycloaddition (SPAAC) chemistry.

38. The pharmaceutical composition of any one of claims 27 to 37, wherein the ApoE polypeptide, or the fragment thereof, and/or the ApoB polypeptide, or the fragment thereof, comprise a dibenzocyclooctyne (DBCO)-functionalized ApoE polypeptide, or fragment thereof, and/or a dibenzocyclooctyne (DBCO)-functionalized ApoB polypeptide, or fragment thereof, represented by the following structure:



;

wherein:

the ApoE polypeptide, or the fragment thereof, comprises an amino acid sequence set forth in EELRVRLASHLRKLRKRLLRDADDLQKGG (SEQ ID NO:3), or an amino acid sequence having a similarity of at least 85% to the amino acid sequence set forth in SEQ ID NO:3; or

the ApoB polypeptide, or the fragment thereof, comprises an amino acid sequence set forth in SSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSGGC (SEQ ID NO:2) or an amino acid sequence having a similarity of at least 85% to the amino acid sequence set forth in SEQ ID NO:2.

39. The pharmaceutical composition of claim 38, which is prepared in combination with an azide compound, wherein the azide compound is DSPE-PEG2000-azide or 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[azido(polyethylene glycol)-2000] or a salt thereof.

40. The pharmaceutical composition of any one of claims 1-12 or 15-39, wherein:
the LNP has a diameter ranging from about 40 nm to about 120 nm;
the LNP has a diameter of less than about 100 nm; or
the LNP has a diameter of about 60 nm to about 80 nm.

41. Use of a pharmaceutical composition of any one of claims 1-12 or 15-40 in the manufacture of a medicament for treating a genetic disorder in a subject in need thereof.

42. The use according to claim 41, wherein the subject is a human.

43. The use according to claim 41 or 42, wherein the disorder is an ocular disorder.

44. The use according to claim 41 or 42, wherein the genetic disorder is selected from the group consisting of: sickle-cell anemia, melanoma, hemophilia A (clotting factor VIII (FVIII) deficiency) and hemophilia B (clotting factor IX (FIX) deficiency), cystic fibrosis (CFTR), familial hypercholesterolemia (LDL receptor defect), hepatoblastoma, Wilson disease, phenylketonuria (PKU), congenital hepatic porphyria, inherited disorders of hepatic metabolism, Lesch Nyhan syndrome, sickle cell anemia, thalassaemias, xeroderma pigmentosum, Fanconi's anemia, retinitis pigmentosa, ataxia telangiectasia, Bloom's syndrome, retinoblastoma, mucopolysaccharide storage diseases (*e.g.*, Hurler syndrome (MPS Type I), Scheie syndrome (MPS Type I S), Hurler-Scheie syndrome (MPS Type I H-S), Hunter syndrome (MPS Type II), Sanfilippo Types A, B, C, and D (MPS Types III A, B, C, and D), Morquio Types A and B (MPS IVA and MPS IVB), Maroteaux-Lamy syndrome (MPS Type VI), Sly syndrome (MPS Type VII), hyaluronidase deficiency (MPS Type IX)), Niemann-Pick Disease Types A/B, C1 and C2, Fabry disease, Schindler disease, GM2-gangliosidosis Type II (Sandhoff Disease), Tay-Sachs disease, Metachromatic Leukodystrophy, Krabbe disease, Mucolipidosis Type I, II/III and IV, Sialidosis Types I and II, Glycogen Storage disease Types I and II (Pompe disease), Gaucher disease Types I, II and III, cystinosis, Batten disease, Aspartylglucosaminuria, Salla disease, Danon disease (LAMP-2 deficiency), Lysosomal Acid Lipase (LAL) deficiency, neuronal ceroid lipofuscinoses (CLN1-8, INCL, and LINCL), sphingolipidoses, galactosialidosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxia, spinal muscular atrophy, Friedreich's ataxia, Duchenne muscular dystrophy (DMD), Becker muscular dystrophies (BMD), dystrophic epidermolysis bullosa (DEB), ectonucleotide pyrophosphatase 1 deficiency, generalized arterial calcification of infancy (GACI), Leber Congenital Amaurosis, Stargardt macular dystrophy (ABCA4), ornithine transcarbamylase (OTC) deficiency, Usher syndrome, age-related macular degeneration (AMD), alpha-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis (PFIC) type I (ATP8B1 deficiency), type II (ABCB11), type III (ABCB4), or type IV (TJP2), LCA10 and Cathepsin A deficiency.

45. Use of a pharmaceutical composition of any one of claims 1-12 or 15-40 in the manufacture of a medicament for:

delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA to the retina of a subject in need thereof; or

delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA to the liver of a subject in need thereof.

46. The use of any one of claims 41-45, wherein the pharmaceutical composition is to be administered by one or more routes selected from the group consisting of: subretinal injection, suprachoroidal injection, and intravitreal injection.

47. A pharmaceutical composition of any one of claims 1-12 or 15-40 for use in therapy.