(Dong, *et al.*, Proc. Natl. Acad. Sci. U.S.A. 111, 3955–3960 (2014)). Although the inclusion of targeting ligands has been shown to enhance the delivery and therapeutic efficiency of mRNA–LNPs, it has been recognized that attaching targeting moieties may add complexity, cost, and regulatory difficulties to the process of manufacturing LNP systems (Cheng *et al.*, Science. 2012 Nov 16; 338(6109):903-10). In addition, it has been demonstrated that the targeting specificity of some targeting ligands may disappear when lipid nanoparticles are exposed to biological fluids where interaction with proteins in the media and the consequent formation of protein corona takes place (Salvati *et al.*, Nat Nanotechnol. 2013 Feb; 8(2):137-43).

[0006] However, to fully realize the potential of nucleic acid therapeutics for ocular diseases and disorders, a targeted, efficient and long-lasting *in vivo* delivery system is needed.

SUMMARY

[0007] AAV vectors are currently the viral vector of choice for retinal gene transfer. However, the optimal method to deliver these treatments to the photoreceptor (PR) cells remains to be improved, with a goal to increase transduction efficacy and to reduce complications associated with the highly invasive surgery required for subretinal injection of the viral vector suspension. 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), while getting into the other layers of the retina where the photoreceptor cells are, has remained a challenge.

[0008] The present disclosure describes for the first time the combination of a LNP incorporating, for example, Lipid A or Lipid 58 as the ionizable lipid, with an mRNA cargo for retinal delivery. Using mouse, rat, and non-human primate (NHP) *in vivo* systems, the present disclosure surprisingly demonstrated that GFP expression can be achieved evenly in the RPE cells (eye cup) and PR cells (neural retina) using LNP/GFP mRNA constructs. Importantly, the data presented herein shows that saturation can be achieved at low doses of LNP/mRNA construct; that is, the dose of LNPs does not need to be high for expression, which is an important consideration for toxicity. The results presented in the instant disclosure surprisingly demonstrate not only are the LNP compositions of the disclosure consistently able to be internalized by the photoreceptor cells, but they are able to do so and achieve satisfactory expression at low doses and without causing toxicity issues such as retinal degradation. The disclosure also provides a pharmaceutical composition comprising a lipid nanoparticle (LNP), a therapeutic nucleic acid (TNA) and at least one pharmaceutically acceptable excipient, wherein the LNP comprises at least one lipid, and wherein the LNP is capable of delivering the TNA to a retinal cell. According to some examples, the LNP is capable of delivering the TNA to a photoreceptor (PR) cell. According to some examples, the LNP is capable of delivering the TNA to a retinal pigment epithelium (RPE) cell. In one aspect, the present disclosure provides a pharmaceutical composition comprising a

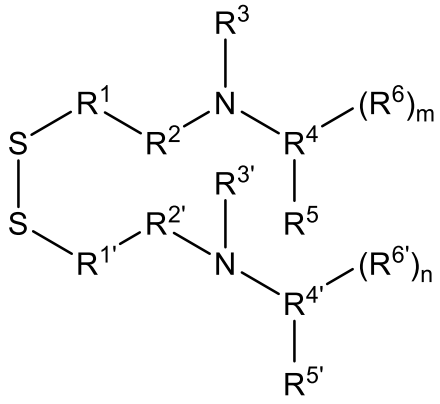
lipid nanoparticle (LNP), a therapeutic nucleic acid (TNA) and at least one pharmaceutically acceptable excipient, wherein the LNP comprises at least one lipid, and wherein the LNP is capable of delivering the TNA to a retinal cell, wherein the retinal cell is a photoreceptor (PR) cell or a retinal pigment epithelium (RPE) cell. According to some examples defined herein, the LNP is capable of delivering the TNA 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 defined herein, the pharmaceutical composition is for administration to a subject. According to some examples, the pharmaceutical composition is for administration to a subject via subretinal injection, suprachoroidal injection, or intravitreal injection. According to some examples , the LNP/TNA is for administration at a dose of about 0.03 μg to about 2.0 μg, for example about 0.03 μg to about 1.5 μg, about 0.05 μg to about 2.0 μg, about 1.0 μg to about 1.5 μg, about 1.0 μg to about 2.0 μg, about 1.5 μg to about 2.0 μg, about 0.5 μg to about 1.0 μg, or about 0.5 μg to about 1.5 μg. According to some examples , the LNP/TNA is for administration at a dose of about 0.1 μg to about 1.0 μg, for example about 0.1 μg to about 0.5 μg or about 0.5 μg to about 1.0 μg or about 0.25 μg to about 0.5 μg or about 0.1 μg to about 0.25 μg or about 0.75 μg to about 1.0 μg. According to some examples , the LNP/TNA is for administration at a dose of about 0.1 μg to about 0.5 μg, for example 0.1 μg, 0.2 μg, 0.25 μg, 0.3 μg, 0.35 μg, 0.4 μg, 0.45 μg or 0.5 μg. According to some examples , the subject is a human in need of treatment with LNP encapsulated with TNA. According to some examples defined herein, the LNP is capable of being internalized into the PR cell and/or the RPE cell. According to some examples defined herein, retinal degeneration does not exceed more than 5% of outer nuclear layer (ONL) loss after 7 days. According to some examples defined herein, retinal degeneration does not exceed more than 5% of outer nuclear layer (ONL) loss after 14 days. According to some examples defined herein, retinal degeneration does not exceed more than 5% of outer nuclear layer (ONL) loss after 21 days. According to some examples defined herein, retinal degeneration does not exceed more than 5% of outer nuclear layer (ONL) loss after 4 weeks. According to some examples defined herein, retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 7 days. According to examples defined herein, retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 14 days. According to some examples defined herein, retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 21 days. According to some examples defined herein, retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 4 weeks. According to some examples defined herein, retinal degeneration does not exceed more than 15% of outer nuclear layer (ONL) loss after 7 days. According to some examples defined herein, retinal degeneration does not exceed more than 15% of outer nuclear layer (ONL) loss after 14 days. According to some examples defined herein, retinal degeneration does not exceed more than 15% of outer nuclear layer (ONL) loss after 21 days. According to some examples defined herein, retinal degeneration does not exceed more than 15% of outer nuclear layer (ONL) loss after 4 weeks. According to some

examples defined herein, ONL loss is measured by Optical Coherence Tomography (OCT). According to some examples defined 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 a PEGylated lipid. According to some examples defined herein, the TNA is encapsulated in the lipid. According to some examples defined herein, 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.

[0009] According to some examples defined herein, the pharmaceutical composition is administered to a subject. According to some examples, the subject is a human patient in need of treatment with the TNA encapsulated by the LNP.

[0010] 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;

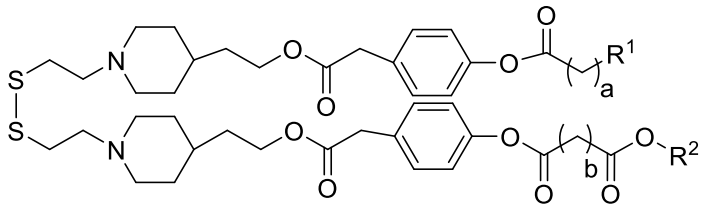
or alternatively, when $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

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.

[0011] According to some examples, the cationic lipid is represented by Formula (II):



(II);

or a pharmaceutically acceptable salt thereof, wherein:

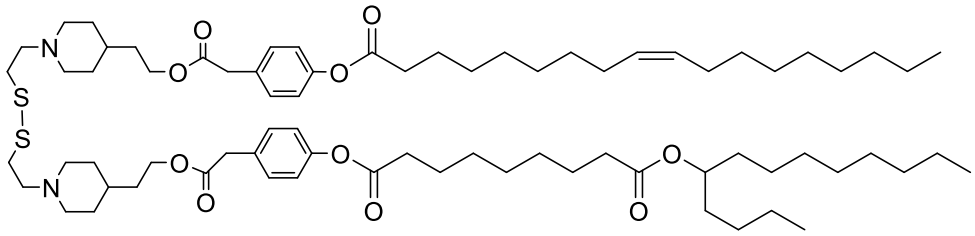
a is an integer ranging from 1 to 20;

b is an integer ranging from 2 to 10;

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

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

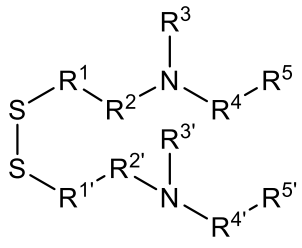
[0012] According to some examples, the cationic lipid is 1-(4-(2-(2-(1-(2-((2-(4-(2-(2-(4-(oleoyloxy)phenyl)acetoxy)ethyl)piperidin-1-yl)ethyl)disulfaneyl)ethyl)piperidin-4-yl)ethoxy)-2-oxoethyl)phenyl) 9-(tridecan-5-yl) nonanedioate (Lipid 58), represented by the following structural formula:



Lipid 58

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[0013] 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;

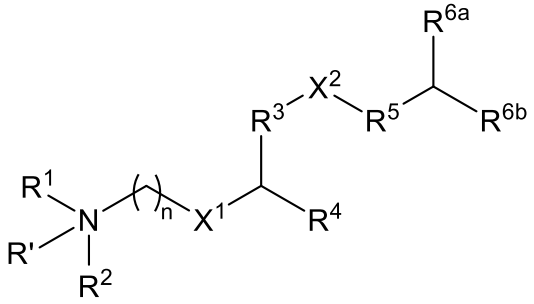
or alternatively, R^2 and R^3 and/or $R^{2'}$ and $R^{3'}$ are taken together with their intervening N atom to form a 4- to 7-membered heterocyclyl;

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.

[0014] According to some examples, the cationic lipid is represented by Formula (XV):



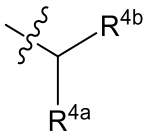
(XV)

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;

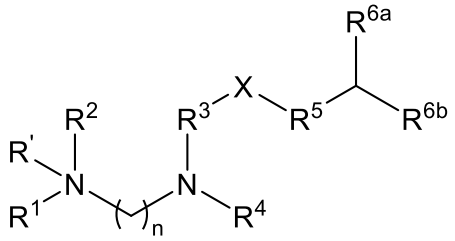
X^1 and X^2 are each independently -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C(R^a)=N-, -N=C(R^a)-, -C(R^a)=NO-, -O-N=C(R^a)-, -C(=O)NR^a-,

-$NR^aC(=O)$-, -$NR^aC(=O)NR^a$-, -$OC(=O)O$-, -$OSi(R^a)_2O$-, -$C(=O)(CR^a_2)C(=O)O$-, 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.

[0015] According to some examples, the cationic lipid is represented by Formula (XX):



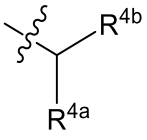
(XX)

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;

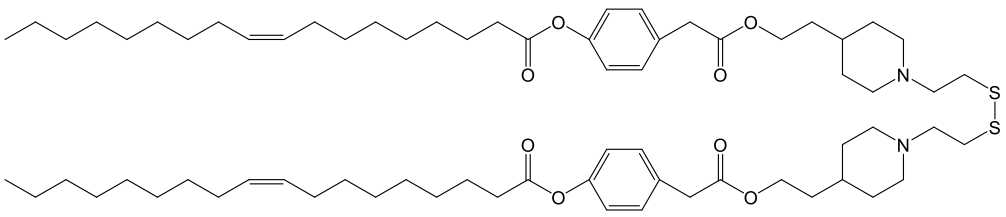
R^{6a} and R^{6b} are each independently C_7-C_{14} alkyl or C_7-C_{14} alkenyl;

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-$N=C(R^a)$-, -$C(=O)NR^a$-, -$NR^aC(=O)$-, -$NR^aC(=O)NR^a$-, -$OC(=O)O$-, -$OSi(R^a)_2O$-, -$C(=O)(CR^a_2)C(=O)O$-, or $OC(=O)(CR^a_2)C(=O)$-; wherein:

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

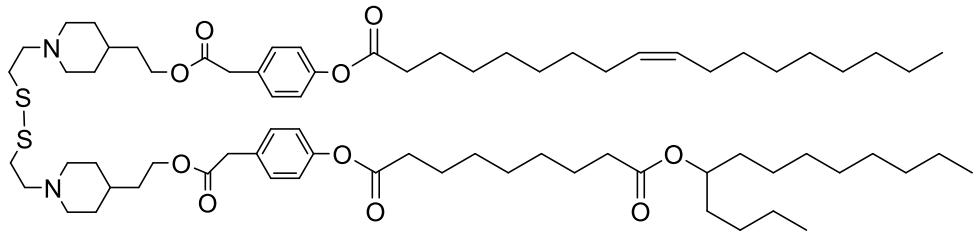
n is an integer selected from 1, 2, 3, 4, 5, and 6. According to some examples, the cationic lipid is selected from any lipid in Table 2, Table 5, Table 6, Table 7, or Table 8.

[0016] According to some examples, the cationic lipid is Lipid A represented by the following structure:



or a pharmaceutically acceptable salt thereof.

[0017] 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

or a pharmaceutically acceptable salt thereof.

[0018] According to some examples, the sterol or a derivative thereof is a cholesterol.

[0019] According to some examples, the sterol or a derivative thereof is beta-sitosterol.

[0020] 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).

[0021] 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), and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-poly(ethylene glycol)-hydroxyl (DSPE-PEG-OH). According to some examples, the PEGylated lipid is DMG-PEG, DSPE-PEG, DSPE-PEG-OH, DSG-PEG, or a combination thereof. According to some examples, the PEGylated lipid is DMG-PEG2000, DSPE-PEG2000, DSPE-PEG2000-OH, DSG-PEG2000, or a combination thereof.

[0022] According to some examples defined herein, the cationic lipid is present at a molar percentage of about 30% to about 80%, for example about 30% to about 70%, about 30% to about 60%, about 30% to about 50%, about 30% to about 40%, about 40% to about 80%, about 40% to about 70%, about 40% to about 60%, about 40% to about 50%, about 50% to about 80%, about 50% to about 70%, about 50% to about 60%, about 60% to about 80%, about 60% to about 70% , or about 70% to about 80%. According to some examples defined herein, the sterol is present at a molar percentage of about 20% to about 50%, about 20% to about 40%, about 20% to about 30%, about 30% to about 50%, about 30% to about 40%, or about 40% to about 50%. According to some examples defined herein, the non-cationic lipid is present at a molar percentage of about 2% to about 20%, for example about 2% to about 15%, about 2% to about 10%, about 2% to about 5%, about 5% to about 20%, about 5% to about 15%, about 5% to about 10%, about 10% to about 15%, about 10% to about 20%, or about 15% to about 20%. According to some examples defined herein, the PEGylated lipid is present at a molar percentage of about 2.1% to about 10%, for example about 2.1% to about 5% or about 5% to about 10% or wherein the PEGylated lipid is present at a molar percentage of about 1% to about 2%, for example about 1%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9% or 2% According to some examples defined herein, the pharmaceutical composition further comprises dexamethasone palmitate. According to some examples, the LNP comprises Lipid A, DOPC, cholesterol and DMG-PEG. According to some examples, the LNP comprises Lipid A, DOPC, cholesterol, DMG-PEG, and DSPE-PEG. According to some examples, the LNP comprises Lipid A, DOPE, cholesterol and DMG-PEG. According to some examples, the LNP comprises Lipid A, DOPE, cholesterol, DMG-PEG, and DSPE-PEG. According to some examples, the LNP comprises Lipid A, DSPC,

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

[0023] According to some examples defined herein, the DMG-PEG is DMG-PEG2000. According to some examples defined herein, the DSPE-PEG is DSPE-PEG2000. According to some examples defined herein, the e DSPE-PEG is DSPE-PEG5000. According to some examples, the LNP comprises Lipid A, DOPC, sterol, DMG-PEG and DSPE-PEG at molar ratios of about 51 : 7.3 : 38.3 : 2.9 : 0.5. According to some examples defined herein, the LNP has a total lipid to TNA ratio of about 10:1 to about 40:1, for example about 10:1, about 15:1, about 20:1, about 25:1 about 30:1, about 35:1, or about 40:1.

[0024] According to other examples, the disclosure provides a method of treating an ocular disorder in a subject, the method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of the examples defined herein. In another aspect, the present disclosure provides use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating an ocular disorder. According to some examples, the subject is a human.

[0025] According to some examples defined herein, the ocular disorder is Stargardt macular dystrophy. According to some examples defined herein, the ocular disorder is LCA10. According to some examples defined herein, the ocular disorder is Usher syndrome. According to some examples defined herein, the ocular disorder is wet AMD.

[0026] According to some examples, 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 of any one of the examples defined herein. According to some examples, the subject is a human. According to some examples, the genetic disorder is an ocular disorder.

[0027] According to some examples, the disclosure provides a method of delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA in the retina of a subject, the method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of any one of the examples defined herein. In yet another aspect, the present disclosure provides the pharmaceutical composition as described herein for use in delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA in the retina of a subject.

[0027a] In yet another aspect, the present disclosure provides the pharmaceutical composition as described herein for use in therapy.

CLAIMS

What is Claimed is:

1. A pharmaceutical composition comprising a lipid nanoparticle (LNP), a therapeutic nucleic acid (TNA) and at least one pharmaceutically acceptable excipient, wherein the LNP comprises at least one lipid, and wherein the LNP is capable of delivering the TNA to a retinal cell, wherein the retinal cell is a photoreceptor (PR) cell or a retinal pigment epithelium (RPE) cell.

2. The pharmaceutical composition of claim 1, wherein expression of the TNA in the PR cell and expression of the TNA in RPE cell is evenly distributed.

3. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is for administration to a subject via a route selected from the group consisting of: subretinal injection, suprachoroidal injection, and intravitreal injection.

4. The pharmaceutical composition of claim 3, wherein the LNP/TNA is for administration at a dose of about 0.03 μg to about 2.0 μg; at a dose of about 0.1 μg to about 1.0 μg; or at a dose of about 0.1 μg to about 0.5 μg.

5. The pharmaceutical composition of any of claims 1-4, wherein:

retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 7 days;

retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 14 days;

retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 21 days; or

retinal degeneration does not exceed more than 10% of outer nuclear layer (ONL) loss after 4 weeks.

6. The pharmaceutical composition of claim 5, wherein ONL loss is measured by Optical Coherence Tomography (OCT).

7. The pharmaceutical composition of any one of claims 1-6, wherein the LNP comprises at least one lipid selected from the group consisting of: a cationic lipid, a sterol or a derivative thereof, a non-cationic lipid, and a PEGylated lipid.

8. The pharmaceutical composition of any one of claims 1-7, wherein the TNA is encapsulated in the lipid.

9. The pharmaceutical composition of any one of claims 1-8, wherein 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, dumbbell linear DNA, dicer-substrate dsRNA, small hairpin RNA (shRNA), asymmetrical interfering RNA (aiRNA), mRNA, tRNA, rRNA, gRNA, DNA viral vectors, viral RNA vector, non-viral vector and any combination thereof.

10. The pharmaceutical composition of claim 9, wherein the TNA is mRNA.

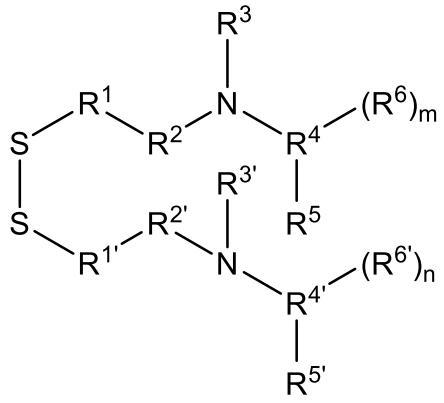
11. The pharmaceutical composition of claim 9, wherein the TNA is siRNA.

12. The pharmaceutical composition of any one of claims 1-11, wherein the pharmaceutical composition is to be administered to a subject.

13. The pharmaceutical composition of claim 12, wherein the subject is a human patient in need of treatment with the TNA encapsulated by the LNP.

14. The pharmaceutical composition of claim 7, wherein:

(a) 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;

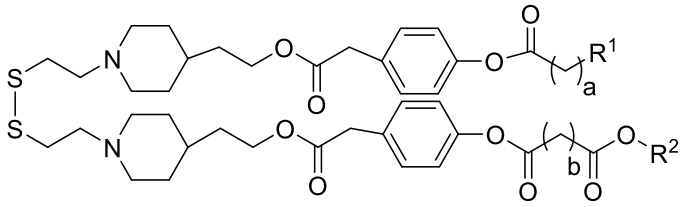
or alternatively, when $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

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;

(b) the cationic lipid is represented by Formula (II):



(II);

or a pharmaceutically acceptable salt thereof, wherein:

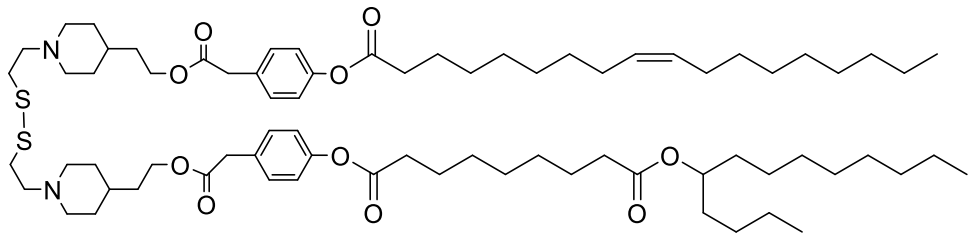
a is an integer ranging from 1 to 20;

b is an integer ranging from 2 to 10;

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

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

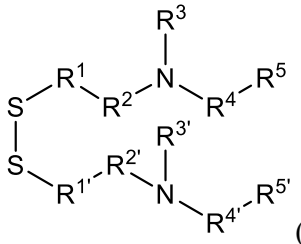
(c) the cationic lipid is 1-(4-(2-(2-(1-(2-((2-(4-(2-(2-(4-(oleoyloxy)phenyl)acetoxy)ethyl)piperidin-1-yl)ethyl)disulfaneyl)ethyl)piperidin-4-yl)ethoxy)-2-oxoethyl)phenyl) 9-(tridecan-5-yl) nonanedioate (Lipid 58), represented by the following structural formula:



Lipid 58

;

(d) the cationic 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;

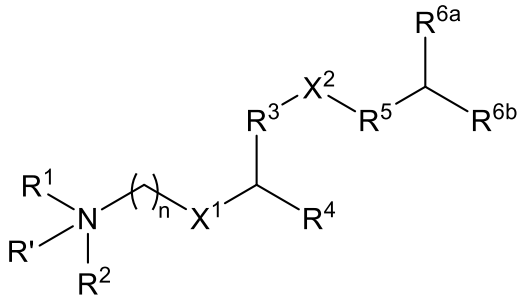
or alternatively, R^2 and R^3 and/or $R^{2'}$ and $R^{3'}$ are taken together with their intervening N atom to form a 4- to 7-membered heterocyclyl;

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;

(e) the cationic lipid is represented by Formula (XV):

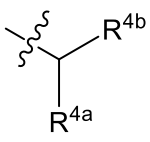

(XV)

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;

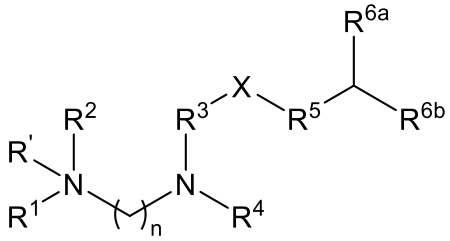
R^{6a} and R^{6b} are each independently C_7-C_{16} alkyl or C_7-C_{16} alkenyl; provided that the total number of carbon atoms in R^{6a} and R^{6b} as combined is greater than 15;

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;

(f) the cationic lipid is represented by Formula (XX):



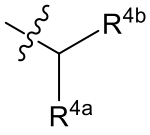
(XX)

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;

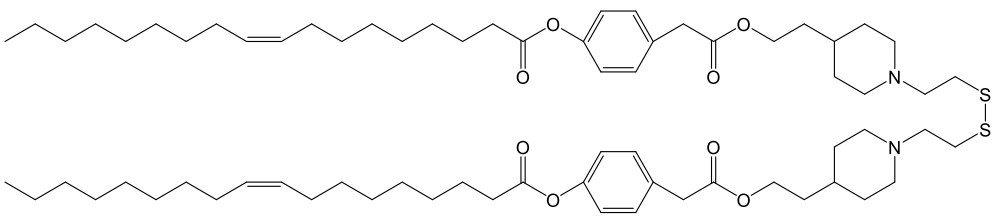
X is -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C(R^a)=N-, -N=C(R^a)-, -C(R^a)=NO-, -O-N=C(R^a)-, -C(=O)NR^a-, -NR^aC(=O)-, -NR^aC(=O)NR^a-, -OC(=O)O-, -OSi(R^a)$_2$O-, -C(=O)(CR^a_2)C(=O)O-, or OC(=O)(CR^a_2)C(=O)-; wherein:

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;

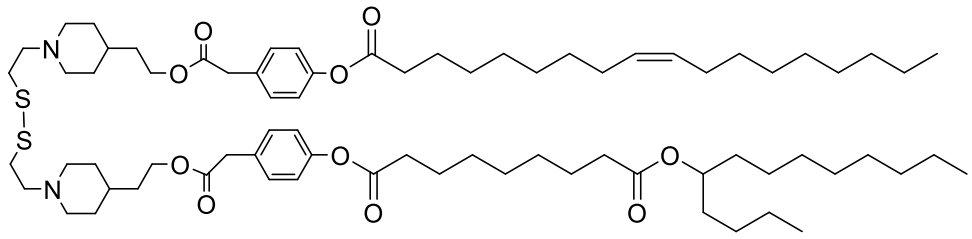
(g) the cationic lipid is selected from the group consisting of the lipids set forth in Table 2, Table 5, Table 6, Table 7, and Table 8;

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



or a pharmaceutically acceptable salt thereof; or

(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

or a pharmaceutically acceptable salt thereof.

15. The pharmaceutical composition of claim 7, wherein the sterol or a derivative thereof is cholesterol or beta-sitosterol.

16. The pharmaceutical composition of claim 7, wherein:

the non-cationic lipid is selected from the group consisting of distearoyl-sn-glycerophosphoethanolamine (DSPE), distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoylphosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoylphosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoylphosphatidylethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoylphosphatidylethanolamine (DSPE), monomethylphosphatidylethanolamine (such as 16-O-monomethyl PE), dimethylphosphatidylethanolamine (such as 16-O-dimethyl PE), 18-1-trans PE, 1-stearoyl-2-oleoylphosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucoylphosphatidylcholine (DEPC), palmitoyloleyolphosphatidylglycerol (POPG), dielaidoylphosphatidylethanolamine (DEPE), 1,2-

dilauroyl-sn-glycero-3-phosphoethanolamine (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; or

the non-cationic lipid is selected from the group consisting of dioleoylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC), and dioleoylphosphatidylethanolamine (DOPE).

17. The pharmaceutical composition of claim 7, wherein:

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), and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-poly(ethylene glycol)-hydroxyl (DSPE-PEG-OH); or

the PEGylated lipid is DMG-PEG, DSPE-PEG, DSPE-PEG-OH, DSG-PEG, or a combination thereof; or

the PEGylated lipid is DMG-PEG2000, DSPE-PEG2000, DSPE-PEG2000-OH, DSG-PEG2000, or a combination thereof.

18. The pharmaceutical composition of claim 14, wherein the cationic lipid is present at a molar percentage of about 30% to about 80%.

19. The pharmaceutical composition of claim 15, wherein the sterol is present at a molar percentage of about 20% to about 50%.

20. The pharmaceutical composition of claim 16, wherein the non-cationic lipid is present at a molar percentage of about 2% to about 20%.

21. The pharmaceutical composition of claim 17, wherein the PEGylated lipid is present at a molar percentage of about 2.1% to about 10% or wherein the PEGylated lipid is present at a molar percentage of about 1% to about 2%.

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

23. The pharmaceutical composition of claim 14, wherein:
the LNP comprises Lipid A, DOPC, cholesterol and DMG-PEG;
the LNP comprises Lipid A, DOPC, cholesterol, DMG-PEG, and DSPE-PEG;
the LNP comprises Lipid A, DOPE, cholesterol and DMG-PEG;
the LNP comprises Lipid A, DOPE, cholesterol, DMG-PEG, and DSPE-PEG;
the LNP comprises Lipid A, DSPC, cholesterol and DMG-PEG;
the LNP comprises Lipid A, DSPC, cholesterol, DMG-PEG, and DSPE-PEG;
the LNP comprises Lipid A, DOPC, beta-sitosterol and DMG-PEG;
the LNP comprises Lipid A, DOPC, beta-sitosterol, DMG-PEG, and DSPE-PEG;
the LNP comprises Lipid A, DOPE, beta-sitosterol and DMG-PEG;
the LNP comprises Lipid A, DOPE, beta-sitosterol, DMG-PEG, and DSPE-PEG;
the LNP comprises Lipid A, DSPC, beta-sitosterol and DMG-PEG; or
the LNP comprises Lipid A, DSPC, beta-sitosterol, DMG-PEG, and DSPE-PEG.

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

25. The pharmaceutical composition of claim 24, wherein the LNP comprises Lipid A, DOPC, sterol, DMG-PEG and DSPE-PEG at molar ratios of about 51 : 7.3 : 38.3 : 2.9 : 0.5.

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

27. Use of the pharmaceutical composition of any one of claims 1 to 26 in the manufacture of a medicament for treating an ocular disorder in a subject.

28. The use according to claim 27, wherein the ocular disorder is selected from the group consisting of: Stargardt macular dystrophy, LCA10, Usher syndrome and wet age-related macular degeneration (AMD).

29. The use according to claim 27 or 28, wherein the subject is a human.

30. The pharmaceutical composition of any one of claims 1 to 26 for use in delivering a therapeutic nucleic acid (TNA) or increasing the concentration of the TNA in the retina of a subject.

31. The pharmaceutical composition of any one of claims 1 to 26 for use in therapy.