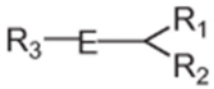
~~CLAIMS~~

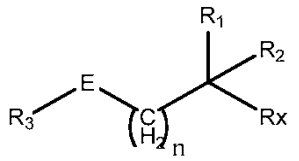
~~We claim:~~

Claims

1. A lipid having the structure



~~XXXIII~~



XXXVIII or ~~salts~~a salt or ~~isomers~~isomer thereof, wherein~~:~~

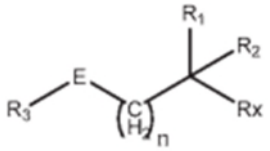
E is C(O)O or OC(O);

R_1 and R_2 and R_x are each independently for each occurrence H, optionally substituted C_1-C_{10}~~-C_{30}~~ alkyl, ~~optionally substituted Cio-C30 alkenyl, optionally substituted C_{10}-C_{30} alkynyl,~~or optionally substituted C_{10}-C_{30} acyl, ~~or linker ligand~~provided that at least one of R_1, R_2 and R_x is not H;

R_3 is ~~H, optionally substituted C_1-C_{10} alkyl,~~ optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, ~~alkylhetrocycle~~alkylheterocycle, alkylphosphate, alkylphosphorothioate, alkylphosphorodithioate, ~~alkylphosphonates, alkylamines, hydroxyalkyls~~alkylphosphonate, alkylamine, hydroxyalkyl, ω-~~aminoalkyls~~aminoalkyl, ω-(substituted)~~aminoalkyls~~aminoalkyl, ω-~~phosphoalkyls~~phosphoalkyl, ω-~~thiophosphoalkyls, optionally substituted polyethylene glycol (PEG, mw 100-40K), optionally substituted mPEG (mw 120-40K),~~thiophosphoalkyl, heteroaryl, or heterocycle~~, or linker ligand~~; and

~~E is C(0)O or OC(0).~~

~~1. A lipid having the structure~~



~~XXXVIII~~

~~or salts or isomers thereof,~~

~~wherein~~

~~E is C(0)O or OC(0);~~

~~R_1 and R_2 and R_x are each independently for each occurrence H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{10}-C_{30} alkyl, optionally substituted C_{10}-C_{30} alkenyl, optionally substituted C_{10}-C_{30} alkynyl, optionally substituted C_{10}-C_{30} acyl, or linker-ligand, provided that at least one of R_1, R_2 and R_x is not H;~~

~~R_3 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, alkylhetrocycle, alkylphosphate, alkylphosphorothioate, alkylphosphorodithioate, alkylphosphonates, alkylamines, hydroxyalkyls, ω-aminoalkyls, ω-(substituted)aminoalkyls, ω-phosphoalkyls, ω-thiophosphoalkyls, optionally substituted polyethylene glycol (PEG, mw 100-40K), optionally substituted mPEG (mw 120-40K), heteroaryl, heterocycle, or linker-ligand;~~

n is 0, 1, 2, or 3.

~~3~~2. A lipid particle comprising a lipid of ~~claims 1or 2~~claim 1, or a salt or isomer thereof.

~~4~~3. The lipid particle of claim ~~3, comprising the lipid of claim 2.~~

~~5. The lipid particle of claim 3~~, wherein the particle further comprises a neutral lipid and a lipid capable of reducing aggregation.

~~6. The lipid particle of claim 5, wherein the lipid particle consists essentially of~~

~~a. Lipid of claim 1 or 2;~~

~~b. a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM;~~

~~c. sterol; and~~

~~d. PEG-DMG,~~

~~in a molar ratio of about 20-60% lipid:5-25% neutral lipid:25-55% stero1:0.5-15% PEG-DMG or PEG-DMA.~~

~~7~~

4. The lipid particle of claim 3, wherein the lipid capable of reducing aggregation is a PEG-lipid.

5. The lipid particle of claim 2, further comprising a therapeutic agent.

~~8~~

6. The lipid particle of claim ~~7~~5, wherein the therapeutic agent is a nucleic acid.

~~9~~

7. The lipid particle of claim ~~8, wherein the nucleic acid is a plasmid.~~

~~10. The lipid particle of claim 8, wherein the nucleic acid is an immunostimulatory oligonucleotide.~~

~~11. The lipid particle of claim 8~~6, wherein the nucleic acid is selected from the group consisting of an siRNA~~,~~ and an antisense oligonucleotide~~, a microRNA, an antagomir, an aptamer, and a ribozyme.~~.

~~12~~

8. The lipid particle of claim ~~11~~6, wherein the nucleic acid is an siRNA.

9. The lipid particle of claim 6, wherein the nucleic acid is an mRNA.

10. A pharmaceutical composition comprising a lipid particle of claim ~~8~~2 and a pharmaceutically acceptable excipient, carrier, or diluent.

~~A method of~~

11. Use of the lipid particle of claim 5 in the manufacture of a medicament for modulating the expression of a target gene in a cell, wherein said medicament is to be provided to the cell.

~~13.~~ 12. Use of the lipid particle of claim 8 in the manufacture of a medicament for modulating the expression of a target gene in a cell, ~~comprising providing to a cell the lipid particle of claim 7.~~

~~14. The method of claim 14,~~ wherein ~~the therapeutic agent is selected from an siRNA, an antagomir, an antisense oligonucleotide, and a plasmid capable of expressing an siRNA, a ribozyme, an aptamer or an antisense oligonucleotide.~~

~~15. The method of claim 14, wherein the nucleic acid~~said medicament is ~~a plasmid that encodes the polypeptide or a functional variant or fragment thereof, such that expression of the polypeptide or the functional variant or fragment thereof is increased.~~

~~16. A method of treating a disease or disorder characterized by overexpression of a polypeptide in a subject, comprising providing to the subject the pharmaceutical composition of claim 13, wherein the therapeutic agent is selected from an siRNA, a microRNA, an antisense oligonucleotide, and a plasmid capable of expressing an siRNA, a microRNA, or an antisense oligonucleotide, and wherein the siRNA, microRNA, or antisense RNA comprises a polynucleotide that specifically binds~~ to ~~a polynucleotide that encodes the polypeptide, or a complement thereof.~~

~~A method of treating a disease or disorder characterized by underexpression of a polypeptide in a subject, comprising providing~~be provided to the ~~subject the pharmaceutical composition of claim 13, wherein the therapeutic agent is a plasmid that encodes the polypeptide or a functional variant or fragment thereof~~cell.

~~17. A method of inducing an immune response in a subject, comprising providing to the subject the pharmaceutical composition of claim 13, wherein the therapeutic agent is an immunostimulatory oligonucleotide.~~

~~18. The method of claim 19, wherein the pharmaceutical composition is provided to the patient in combination with a vaccine or antigen.~~

~~A vaccine comprising~~

13. Use of the lipid particle of claim 9 ~~and an antigen associated with a disease or pathogen~~in the manufacture of a medicament for modulating the expression of a target gene in a cell, wherein said medicament is to be provided to the cell.

14. The lipid particle of claim 3, wherein the neutral lipid is a phospholipid.

15. The lipid particle of claim 3, wherein the particle further comprises a sterol.

16. The lipid particle of claim 15, wherein the sterol is cholesterol.