WHAT IS CLAIMED IS

1. A nucleic acid-lipid particle, said nucleic acid-lipid particle comprising:
an interfering RNA;
a cationic lipid;
a non-cationic lipid; and
a conjugated lipid that inhibits aggregation of particles.

2. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA comprises about 15 to about 60 nucleotides.

3. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA comprises about 15 to about 30 nucleotides.

4. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA is chemically synthesized.

5. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA is transcribed from a plasmid encapsulated in said particle.

6. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA silences the expression of a gene associated with a metabolic disease or disorder.

7. The nucleic acid-lipid particle of claim 6, wherein said interfering RNA silences Apolipoprotein B (ApoB) expression.

8. The nucleic acid-lipid particle of claim 6, wherein said metabolic disease or disorder is dyslipidemia.

9. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA silences the expression of a gene associated with tumorigenesis or cell transformation.

10. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA is fully encapsulated in said particle.

11. The nucleic acid-lipid particle of claim 1, wherein said interfering RNA is resistant in aqueous solution to degradation by a nuclease.

12. The nucleic acid-lipid particle of claim 1, wherein said particle has a median diameter of less than about 150 nm.

13. The nucleic acid-lipid particle of claim 1, wherein said particle has a median diameter of less than about 100 nm.

14. The nucleic acid-lipid particle of claim 1, wherein said cationic lipid is a member selected from the group consisting of N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleyloxypropylamine (DODMA), and combinations thereof.

15. The nucleic acid-lipid particle of claim 1, wherein said non-cationic lipid is a member selected from the group consisting of dioleoylphosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), egg phosphatidylcholine (EPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), cholesterol, and combinations thereof.

16. The nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles is a member selected from the group consisting of a polyethyleneglycol (PEG)-lipid conjugate, a polyamide (ATTA)-lipid conjugate, and combinations thereof.

17. The nucleic acid-lipid particle of claim 1, wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol-lipid and the PEG-

lipid is member selected from the group consisting of a PEG-diacylglycerol (DAG), a PEG dialkyloxypropyl, a PEG-phospholipid, a PEG-ceramide, and combinations thereof.

18. The nucleic acid-lipid particle of claim 17, wherein the conjugated lipid that inhibits aggregation of particles comprises a polyethyleneglycol (PEG)-dialkyloxypropyl conjugate.

19. The nucleic acid-lipid particle of claim 18, wherein the PEG-dialkyloxypropyl conjugate is a member selected from the group consisting of a PEG-dilauryloxypropyl (Cl2) conjugate, a PEG-dimyristyloxypropyl (Cl4) conjugate, a PEG-dipalmityloxypropyl (Cl6) conjugate, a PEG-distearyloxypropyl (C18) conjugate, and combinations thereof.

20. The nucleic acid-lipid particle of claim 1, wherein said cationic lipid comprises from about 2% to about 60% of the total lipid present in said particle.

21. The nucleic acid-lipid particle of claim 1, wherein said cationic lipid comprises from about 5% to about 45% of the total lipid present in said particle.

22. The nucleic acid-lipid particle of claim 1, wherein said cationic lipid comprises from about 5% to about 15% of the total lipid present in said particle.

23. The nucleic acid-lipid particle of claim 1, wherein said cationic lipid comprises from about 40% to about 50% of the total lipid present in said particle.

24. The nucleic acid-lipid particle of claim 1, wherein said non-cationic lipid comprises from about 5% to about 90% of the total lipid present in said particle.

25. The nucleic acid-lipid particle of claim 1, wherein said non-cationic lipid comprises from about 20% to about 85% of the total lipid present in said particle.

26. The nucleic acid-lipid particle of claim 1, wherein said conjugated lipid that inhibits aggregation of particles comprises from about 0.5% to about 50% of the total lipid present in said particle.

27. The nucleic acid-lipid particle of claim 1, wherein said conjugated lipid that inhibits aggregation of particles comprises from about 0.5% to about 25% of the total lipid present in said particle.

28. The nucleic acid-lipid particle of claim 1, wherein said conjugated lipid that inhibits aggregation of particles comprises from about 1% to about 20% of the total lipid present in said particle.

29. The nucleic acid-lipid particle of claim 1, wherein said conjugated lipid that inhibits aggregation of particles comprises from about 3% to about 15% of the total lipid present in said particle.

30. The nucleic acid-lipid particle of claim 1, wherein said conjugated lipid that inhibits aggregation of particles comprises from about 4% to about 10% of the total lipid present in said particle.

31. The nucleic acid-lipid particle of claim 1, wherein said nucleic acid-lipid particle further comprises cholesterol.

32. The nucleic acid-lipid particle of claim 31, wherein the cholesterol comprises from about 10% to about 60% of the total lipid present in said particle.

33. The nucleic acid-lipid particle of claim 31, wherein the cholesterol comprises from about 20% to about 45% of the total lipid present in said particle.

34. The nucleic acid-lipid particle of claim 1, wherein said non-cationic lipid comprises a phospholipid and cholesterol, and wherein said conjugated lipid that inhibits aggregation of particles comprises a PEG-lipid conjugate.

35. The nucleic acid-lipid particle of claim 1, wherein said particle has an interfering RNA:lipid ratio (mg:mg) of from about 0.01 to about 0.08.

36. The nucleic acid-lipid particle of claim 1, wherein said particle has an interfering RNA:lipid ratio (mg:mg) of about 0.04.

37. The use of a nucleic acid-lipid particle to formulate a composition for introducing an interfering RNA into a cell, wherein said nucleic acid-lipid particle comprises:

an interfering RNA;

a cationic lipid;

a non-cationic lipid; and

a conjugated lipid that inhibits aggregation of particles.

38. The use of claim 37, wherein the presence of said nucleic acid-lipid particle in target cells is detectable at least 48 hours after administration of said particle.

39. The use of claim 37, wherein the presence of said nucleic acid-lipid particle is detectable at least 24 hours after administration of said particle.

40. The use of claim 37, wherein said cell is in a mammal.

41. The use of claim 37, wherein said cell is a hepatocyte.

42. The use of claim 37, wherein said cell is a neoplastic cell.

43. The use of claim 40, wherein more than 10% of said particles are present in the plasma of said mammal 24 hours after administration.

44. The use of claim 40, wherein the presence of said interfering RNA at a site distal to the site of administration is detectable for at least 48 hours after administration of said particle.

45. The use of claim 40, wherein the presence of said interfering RNA at a site distal to the site of administration is detectable for at least 24 hours after administration of said particle.

46. The use of claim 40, wherein the mammal is a human.

47. The use of claim 37, wherein said particle has the features of any of claims 2-36.

48. The use of a nucleic acid-lipid particle to formulate a medicament for silencing the expression of a target sequence in a mammal, wherein said nucleic acid-lipid particle comprises:

an interfering RNA;

a cationic lipid;

a non-cationic lipid; and

a conjugated lipid that inhibits aggregation of particles.

49. The use of claim 48, wherein said nucleic acid-lipid particle is formulated for intravenous administration.

50. The use of claim 48, wherein said mammal is a human.

51. The use of claim 50, wherein said human has a disease or disorder associated with expression of a gene comprising a target sequence for said interfering RNA.

52. The use of claim 51, wherein said disease or disorder is associated with overexpression of said gene.

53. The use of claim 51, wherein said disease or disorder is dyslipidemia.

54. The use of claim 51, wherein said disease or disorder is cancer.

55. The use of claim 48, wherein said particle has the features of any of claims 2-36.

56. The use of a nucleic acid-lipid particle to formulate a medicament for the *in vivo* delivery of an interfering RNA, wherein said nucleic acid-lipid particle comprises:

an interfering RNA;

a cationic lipid;

a non-cationic lipid; and

a conjugated lipid that inhibits aggregation of particles.

57. The use of claim 56, wherein said nucleic acid-lipid particle is formulated for intravenous administration.

58. The use of claim 56, wherein said mammal is a human.

59. The use of claim 58, wherein said human has a disease or disorder associated with expression of a gene comprising a target sequence for said interfering RNA.

60. The use of claim 59, wherein said disease or disorder is associated with overexpression of said gene.

61. The use of claim 59, wherein said disease or disorder is dyslipidemia.

62. The use of claim 59, wherein said disease or disorder is cancer.

63. The use of claim 56, wherein said particle has the features of any of claims 2-36.

64. The use of a nucleic acid-lipid particle to formulate a medicament for the *in vivo* delivery of an interfering RNA to a liver cell, wherein said nucleic acid-lipid particle comprises:

an interfering RNA;

a cationic lipid;

a non-cationic lipid; and

a conjugated lipid that inhibits aggregation of particles.

65. The use of claim 64, wherein said nucleic acid-lipid particle is formulated for intravenous administration.

66. The use of claim 64, wherein said mammal is a human.

67. The use of claim 66, wherein said human has a disease or disorder associated with expression of a gene comprising a target sequence for said interfering RNA.

68. The use of claim 67, wherein said disease or disorder is associated with overexpression of said gene.

69. The use of claim 67, wherein said disease or disorder is dyslipidemia.

70. The use of claim 67, wherein said disease or disorder is cancer.

71. The use of claim 64, wherein said particle has the features of any of claims 2-36.

72. The use of a nucleic acid-lipid particle to formulate a medicament for treating a disease or disorder in a mammal, wherein said nucleic acid-lipid particle comprises:

an interfering RNA;

a cationic lipid;

a non-cationic lipid; and

a conjugated lipid that inhibits aggregation of particles, wherein said disease or disorder is associated with expression of a gene comprising a target sequence for said interfering RNA.

73. The use of claim 72, wherein said medicament is adapted for intravenous administration.

74. The use of claim 72, wherein said mammal is a human.

75. The use of claim 72, wherein said disease or disorder is associated with overexpression of said gene.

76. The use of claim 72, wherein said disease or disorder is dyslipidemia.

77. The use of claim 72, wherein said disease or disorder is cancer.

78. The use of claim 72, wherein said particle has the features of any of claims 2-36.

CLAIMS

1. A nucleic acid-lipid particle, said nucleic acid-lipid particle comprising:

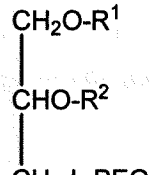
an mRNA;

a cationic lipid;

a non-cationic lipid; and

a polyethyleneglycol (PEG)-lipid conjugate,

wherein the PEG-lipid conjugate comprises a polyethyleneglycol-dialkyloxypropyl (PEG-DAA) conjugate having the following structure:




(I)

wherein $R^1$ and $R^2$ are independently selected from the group consisting of alkyl groups having from 10 to 22 carbon atoms, and

wherein L is a linker moiety selected from the group consisting of amido, amino, carbonyl, carbonate, carbamate, urea, succinyl, ether, and disulphide,

wherein said mRNA is fully encapsulated in said nucleic acid-lipid particle.

2. The nucleic acid-lipid particle of claim 1, wherein said mRNA is resistant in aqueous solution to degradation by a nuclease.

3. The nucleic acid-lipid particle of claim 1 or 2, wherein said particle has a median diameter of less than 150 nm.

4. The nucleic acid-lipid particle of claim 3, wherein said particle has a median diameter of less than 100 nm.

5. The nucleic acid-lipid particle of any one of claims 1 to 4, wherein said cationic lipid is a member selected from the group consisting of N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA),

N,N-dimethyl-2,3-dioleyloxypropylamine (DODMA), and combinations thereof.

6. The nucleic acid-lipid particle of any one of claims 1 to 5, wherein said non-cationic lipid is a member selected from the group consisting of dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), egg phosphatidylcholine (EPC), distearoylphosphatidylcholine (DSPC), cholesterol, and combinations thereof.

7. The nucleic acid-lipid particle of any one of claims 1 to 6, wherein said PEG-DAA conjugate is a PEG-dilauryloxypropyl (C12), a PEG- dimyristyloxypropyl (C14), a PEG-dipalmityloxypropyl (C16), a PEG-distearyloxypropyl (C18), or a combination thereof.

8. The nucleic acid-lipid particle of any one of claims 1 to 7, wherein said cationic lipid comprises from 2% to 60%, from 5% to 45%, from 5% to 15%, or from 40% to 50% of the total lipid present in said particle.

9. The nucleic acid-lipid particle of any one of claims 1 to 8, wherein said non-cationic lipid comprises from 5% to 90% or from 20% to 85% of the total lipid present in said particle.

10. The nucleic acid-lipid particle of any one of claims 1 to 9, wherein said PEG-lipid conjugate comprises from 0.5% to 50%, from 0.5% to 25%, from 1% to 20%, from 3% to 15%, or from 4% to 10% of the total lipid present in said particle.

11. The nucleic acid-lipid particle of any one of claims 1 to 10, wherein said non-cationic lipid comprises a phospholipid and cholesterol.

12. The nucleic acid-lipid particle of claim 11, wherein the cholesterol comprises from 10% to 60% or from 20% to 45% of the total lipid present in said particle.

13. The nucleic acid-lipid particle of any one of claims 1 to 12, wherein said mRNA is chemically synthesized.

14. The nucleic acid-lipid particle of any one of claims 1 to 13, wherein said particle has an mRNA:lipid ratio (mass/mass) of from 0.01 to 0.08 or 0.04.

15. A composition for introducing an mRNA into a cell comprising a nucleic acid-lipid particle, wherein said nucleic acid-lipid particle comprises:

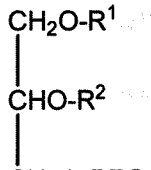
an mRNA;

a cationic lipid;

a non-cationic lipid; and

a polyethyleneglycol (PEG)-lipid conjugate

wherein the PEG-lipid conjugate comprises a polyethyleneglycol-dialkyloxypropyl (PEG-DAA) conjugate having the following structure:




(I)

wherein $R^1$ and $R^2$ are independently selected from the group consisting of alkyl groups having from 10 to 22 carbon atoms, and

wherein L is a linker moiety selected from the group consisting of amido, amino, carbonyl, carbonate, carbamate, urea, succinyl, ether, and disulphide,

wherein said mRNA is fully encapsulated in said nucleic acid-lipid particle.

16. The composition of claim 15, wherein the presence of said nucleic acid-lipid particle in target cells is detectable at least 48 hours or at least 24 hours after administration of said particle.

17. The composition of claim 15 or 16, wherein said cell is in a mammal.

18. The composition of claim 17, wherein more than 10% of said particles are present in plasma of said mammal 24 hours after administration.

19. The composition of claim 17 or 18, wherein the presence of said mRNA at a site distal to the site of administration is detectable for at least 48 hours or at least 24 hours after administration of said particle.

20. The composition of any one of claims 17 to 19, wherein said mammal is a human.

21. A medicament for in vivo delivery of mRNA in a mammal comprising a nucleic acid-lipid particle, wherein said nucleic acid-lipid particle comprises:

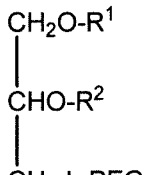
an mRNA;

a cationic lipid;

a non-cationic lipid; and

a polyethyleneglycol (PEG)-lipid conjugate.

wherein the PEG-lipid conjugate comprises a polyethyleneglycol-dialkyloxypropyl (PEG-DAA) conjugate having the following structure:



(I)

wherein $R^1$ and $R^2$ are independently selected from the group consisting of alkyl groups having from 10 to 22 carbon atoms, and

wherein L is a linker moiety selected from the group consisting of amido, amino, carbonyl, carbonate, carbamate, urea, succinyl, ether, and disulphide,

wherein said mRNA is fully encapsulated in said nucleic acid-lipid particle.

22. The medicament of claim 21, wherein said nucleic acid-lipid particle is formulated for intravenous administration.

23. The medicament of claim 21 or 22, wherein said mammal is a human.

24. A medicament for in vivo delivery of mRNA to a liver cell of a mammal comprising a nucleic acid-lipid particle, wherein said nucleic acid-lipid particle comprises:

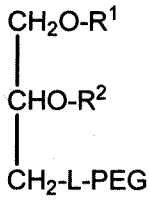
an mRNA;

a cationic lipid;

a non-cationic lipid; and

a polyethyleneglycol (PEG)-lipid conjugate.

wherein the PEG-lipid conjugate comprises a polyethyleneglycol-dialkyloxypropyl (PEG-DAA) conjugate having the following structure:



(I)

wherein $R^1$ and $R^2$ are independently selected from the group consisting of alkyl groups having from 10 to 22 carbon atoms, and

wherein L is a linker moiety selected from the group consisting of amido, amino, carbonyl, carbonate, carbamate, urea, succinyl, ether, and disulphide,

wherein said mRNA is fully encapsulated in said nucleic acid-lipid particle.

25. The medicament of claim 24, wherein said mammal is a human.

26. The medicament of claim 24 or 25, wherein said medicament is for intravenous administration.

27. A medicament for treating a disease in a mammalian subject comprising a nucleic acid-lipid particle, wherein said nucleic acid-lipid particle comprises:

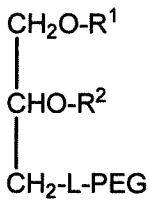
an mRNA;

a cationic lipid;

a non-cationic lipid; and

a polyethyleneglycol (PEG)-lipid conjugate,

wherein the PEG-lipid conjugate comprises a polyethyleneglycol-dialkyloxypropyl (PEG-DAA) conjugate having the following structure:



(I)

wherein $R^1$ and $R^2$ are independently selected from the group consisting of alkyl groups having from 10 to 22 carbon atoms, and

wherein L is a linker moiety selected from the group consisting of amido, amino, carbonyl, carbonate, carbamate, urea, succinyl, ether, and disulphide,

wherein said mRNA is fully encapsulated in said nucleic acid-lipid particle.

28. The medicament of claim 27, wherein said mammal is a human.

29. The medicament of claim 27 or 28, wherein said medicament is for intravenous administration.

30. The composition of claim 15, wherein said particle is the nucleic acid-lipid particle of any one of claims 1 to 14.

31. The medicament of claim 21, wherein said particle is the nucleic acid-lipid particle of any one of claims 1 to 14.

32. The medicament of claim 24, wherein said particle is the nucleic acid-lipid particle of any one of claims 1 to 14.

33. The medicament of claim 27, wherein said particle is the nucleic acid-lipid particle of any one of claims 1 to 14.