We claim:

1. A composition comprising at least one cationic lipid, at least one helper lipid and at least one stealth lipid for delivery of a biologically active agent, wherein the biologically active agent is for delivery to a tissue or cell selected from:

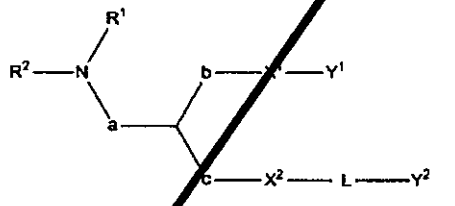
a) a liver or liver cells, wherein the composition has a cationic lipid with a pKa of from about 6.2 or above;

b) a tumor or tumor cell, wherein the composition has a cationic lipid with a pKa of from about 6.2 or below;

c) a liver or liver cells, wherein the composition has a cationic lipid with a pKa of from about 5.1 to about 7.4; and

d) a tumor or tumor cell, wherein the composition has a cationic lipid with a pKa of from about 5.0 to about 6.7.

2. A compound of formula (I):



(I)

or a salt or pharmaceutically acceptable derivative thereof,

wherein:

R^1 and R^2 together with the nitrogen atom to which they are attached form an optionally substituted C_{3-20}-heterocycloalkyl, C_{3-20}-heterocycloalkenyl, C_{3-20}-heterocycloalkynyl or C_{5-20}-heteroaryl group;

a is absent or optionally substituted C_{1-4} alkylene;

b is absent or optionally substituted C_{1-4} alkylene;

c is absent or optionally substituted C_{1-4} alkylene;

X^1 is O or S;

X^2 is O or S;

Y^1 is optionally substituted C_{10-30}alkenyl, C_{10-30}alkynyl, C_{10-30}heteroalkenyl or C_{10-30}heteroalkynyl;

L is absent or $-(L^a)_d-(L^b)_e-(L^c)_f-$, wherein

L^a is optionally substituted C_{1-15}alkylene, C_{1-15}alkenylene, C_{1-15}alkynylene, C_{1-15}heteroalkylene, C_{1-15}heteroalkenylene or C_{1-15}heteroalkynylene;

L^b is optionally substituted C_{6-14}arylene or C_{5-13}heteroarylene;

L^c is optionally substituted C_{1-15}alkylene, C_{1-15}alkenylene, C_{1-15}alkynylene, C_{1-15}heteroalkylene, C_{1-15}heteroalkenylene or C_{1-15}heteroalkynylene;

d is 0 or 1;

e is 0 or 1; and

f is 0 or 1; and

Y^2 is an optionally substituted steroid.

3. The compound of claim 2, wherein one or more substituents are selected from one or more the following:

(a) **a** is selected from optionally substituted C_{1-2} alkylene and optionally substituted C_1 alkylene;

(b) **b** is selected from optionally substituted C_{0-2} alkylene and optionally substituted C_1 alkylene;

(c) **c** is absent or is optionally substituted C_1 alkylene; and/or

(d) **a**, **b** and **c** are unsubstituted.

(e) R^1 and R^2 together with the nitrogen atom to which they are attached form an optionally substituted C_{3-20}-heterocycloalkyl, C_{3-20}-heterocycloalkenyl or C_{3-20}-heterocycloalkynyl group;

(f) wherein R^1 and R^2 together with the nitrogen atom to which they are attached form a compound selected from a cyclic optionally substituted C_{5-16} group and a cyclic optionally substituted C_{5-12} group;

(g) R^1 and R^2 together with the nitrogen atom to which they are attached form a cyclic optionally substituted C_5 group, C_6 group or C_7 group; and

(h) R^1 and R^2 together with the nitrogen atom to which they are attached are selected from at least one of the head groups H^1 to H^{52}.

(i) wherein X^1 is O;

(j) wherein X^2 is O;

(k) wherein both X^1 and X^2 is O;

(l) wherein L comprises at least one heteroatom;

(m) wherein L comprises at least one O atom;

(n) wherein L^c is selected from one of formulae $L^{c\text{-}i}$ to $L^{c\text{-}xxxiii}$.

(o) wherein **d** is 0; **e** is 0, and **f** is 1;

(p) wherein Y^1 is a C_{12-28} group;

(q) wherein Y^1 has at least one alkene group;

(r) wherein Y^1 has at least one cis unsaturated alkene group;

(s) wherein Y^1 is selected from $Y^{1\text{-}i}$ to $Y^{1\text{-}vii}$;

(t) wherein Y^2 is linked to L via an oxygen atom on the optionally substituted steroid;

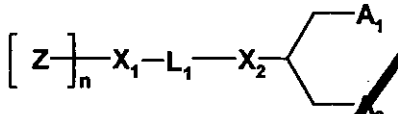
(u) wherein Y^2 is a sterol in which the hydrogen atom of the hydroxy group at the 3-position of the A steroid ring has been removed;

(v) wherein Y^2 is the sterol of part (u), and the sterol is selected from the group consisting of:

annasterol; avenasterol; beta-sitosterol; brassicasterol; calciferol; campesterol; chalinosterol; chinasterol; cholestanol; cholesterol; coprostanol; cycloartenol; dehydrocholesterol; desmosterol; dihydrocalciferol; dihydrocholesterol; dihydroergosterol; dinosterol; epicholesterol; ergosterol; fucosterol; hexahydrolumisterol; hexaol; hydroxycholesterol; lanosterol; lumisterol; parkeol; poriferasterol; saringosterol; sitostanol; sitosterol; stigmastanol; stigmasterol; weinbersterol; zymosterol; sterol bile acids (including one or more selected from cholic acid; chenodeoxycholic acid; glycocholic acid; taurocholic acid; deoxycholic acid, and lithocholic acid); and/or a salt or a pharmaceutically acceptable derivative thereof; and

(w) wherein Y^2 is a cholesterol.

4. A stealth lipid of formula (XI)



(XI)

or a salt or pharmaceutically acceptable derivative thereof,

wherein

Z is a hydrophilic head group component selected from PEG and polymers based on poly(oxazoline), poly(ethylene oxide), poly(vinyl alcohol), poly(glycerol), poly(N-vinylpyrrolidone), poly[N-(2-hydroxypropyl)methacrylamide] and poly(amino acid)s, wherein the polymer may be linear or branched, and wherein the polymer may be optionally substituted;

wherein Z is polymerized by n subunits;

n is a number-averaged degree of polymerization between 10 and 200 units of Z, wherein n is optimized for different polymer types;

L_1 is an optionally substituted $C_{1\text{-}10}$ alkylene or $C_{1\text{-}10}$ heteroalkylene linker including zero, one, two or more of an ether (e.g., -O-), ester (e.g., -C(O)O-), succinate (e.g., -O(O)C-CH_2-CH_2-C(O)O-)), carbamate (e.g., -OC(O)-NR'-), carbonate (e.g., -OC(O)O-), ketone (e.g., -C-C(O)-C-), carbonyl (e.g., -C(O)-), urea (e.g., -NRC(O)NR'-), amine (e.g., -NR'-), amide (e.g., -C(O)NR'-), imine (e.g., -C(NR')-), thioether (e.g., -S-), xanthate (e.g., -OC(S)S-), and phosphodiester (e.g., -OP(O)$_2$O-); any of which may be substituted by zero, one or more Z groups;

wherein R' is independently selected from H, –NH-, -O-, -S-, a phosphate or an optionally substituted $C_{1\text{-}10}$ alkylene;

X_1 and X_2 are independently selected from a carbon or a heteroatom selected from –NH-, -O-, -S- or a phosphate;

A_1 and A_2 are independently selected from a $C_{6\text{-}30}$ alkyl, $C_{6\text{-}30}$ alkenyl, and $C_{6\text{-}30}$ alkynyl, wherein A_1 and A_2 may be the same or different,

or wherein A_1 and A_2 together with the carbon atom to which they are attached form an optionally substituted steroid.

5. The composition of any one or more of claims 2 through 4 for use in the composition of claim 1.

6. The composition of claims 1 or 5, wherein the biologically active agent is for delivery to the liver or a liver cell and the cationic lipid has a pKa selected from at least:
(a) about 5.1 to about 7.4;
(b) about 5.3 to about 7.3;
(c) about 5.9 to about 7.0;
(d) about 6.2 to about 6.8; and
(e) about 6.1 or above

7. The composition of claims 1 or 5, wherein the biologically active agent is for delivery to a tumor or tumor cells and the cationic lipid has a pKa selected from at least:
(a) about 5.0 to about 6.7;
(b) about 5.2 to about 6.3;
(c) about 5.4 to about 6.2;
(d) about 5.8 to about 6.1; and
(e) about 6.1 or below.

8. The composition of any one of claim 1 or claims 5 through 7, said composition further comprising at least one neutral lipid.

9. The composition of any one of claim 1 or claims 5 through 8, wherein the composition is optimized by selection of at least one of a stealth lipid, formulation method, N/P ratio, particle size, and molar ratio of the cationic lipid, an optional neutral lipid, helper lipid, stealth lipid and an optional alkyl resorcinol based lipid.

10. The composition of any one of claim 1 or claims 5 through 9, wherein the cationic lipid is selected from E0001-E0171 and E0175-E0180.

11. The composition of any one of claim 1 or claims 5 through 10, wherein the stealth lipid is selected from S001-S009 and S012-S026.

12. The composition of any one of claim 1 or claims 5 through 11, wherein the composition is optimized for at least one parameter including but not limited to individual selection of the

pKa of the cationic lipid optimized for the type of cell or organ being targeted, the cationic lipid used, the stealth lipid used, the helper lipid, the neutral lipid used, whether the neutral lipid is present or absent, the ratio of the selected helper lipid, optional neutral lipid, stealth lipid and cationic lipid, the N/P ratio, the particle size, the dosage regiment, the dose given, the formulation method, and the like.

13. The composition of any one of claims 1 or claims 5 through 12, further comprising a biologically active agent.

14. The composition of claim 13, wherein the composition comprises a biologically active agent in an amount effective for therapeutic treatment of a disease or disorder.

15. The composition of claims 13 or 14, wherein said biologically active agent is selected from the group consisting of antibodies, cholesterol, hormones, antivirals, peptides, polypeptides, proteins, nucleoproteins, chemotherapeutics, low molecular weight drugs, vitamins, co-factors, nucleosides, nucleoside derivatives, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A antisense chimeras, allozymes, aptamers, decoy RNA molecules and analogs thereof, and small nucleic acid molecules, such as an RNA interfering agent (RNAi), short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA).

16. The composition of claim 15 wherein said biologically active agent is selected from one or more of a nucleoside or nucleoside derivative, an RNAi, an siNA, an RNAi inhibitor, a miRNA, an siRNA and a shRNA.

17. Any one or more of the above compounds, formulations and/or compositions, that further comprises a pharmaceutically acceptable carrier.

18. A kit comprising any one or more of the above compounds, formulations and compositions, and instructions for use.

19. A method for the treatment of a disease or condition comprising the step of administering a therapeutically effective amount of a composition of any of claims 1 or 5 to 17 to a patient in need thereof.

20. The method of claim 19 wherein the disease or condition is a cancer, a disease of the liver, or a disease that is responsive to treatment with an RNAi construct.

21. A method for the treatment of a disease or condition in a subject in need thereof, the method comprising the step of administering a therapeutically effective amount of a biologically active agent in a formulation comprising one or more compositions of any of claims 1 or 5 to 17.

22. The method of claim 21 wherein the disease or condition is a tumor, a disease of the liver, or a disease that is responsive to treatment with an RNAi construct.

CLAIMS

1. An invention not claimed in any divisional application.