Y is O, S, or NR^Y, wherein R^Y is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

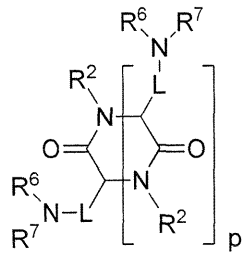
R^P is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, or a nitrogen protecting group when attached to a nitrogen atom; and

R^L is optionally substituted C_{1-50} alkyl, optionally substituted C_{2-50} alkenyl, optionally substituted C_{2-50} alkynyl, optionally substituted heteroC_{1-50} alkyl, optionally substituted heteroC_{2-50} alkenyl, optionally substituted heteroC_{2-50} alkynyl, or a polymer.

[0006] In another aspect, the present invention provides methods of treating a disease or disorder including administering to subject in need of treatment a composition comprising an mRNA encoding a therapeutic protein encapsulated within a liposome such that the administering of the composition results in the expression of the protein encoded by the mRNA in one or more tissues affected by the disease or disorder, wherein the liposome comprises a cationic lipid having a structure of formula I-c.

[0007] In another aspect, the present invention provides compositions for delivery of messenger RNA (mRNA) comprising an mRNA encoding a protein encapsulated within a liposome, wherein the liposome comprises a cationic lipid having a structure of formula I-c.

[0007a] In another aspect, there is provided the use of a composition comprising an mRNA encoding a therapeutic protein encapsulated within a liposome wherein the liposome comprises a cationic lipid of formula I-c:



I-c

or a pharmaceutically acceptable salt thereof,

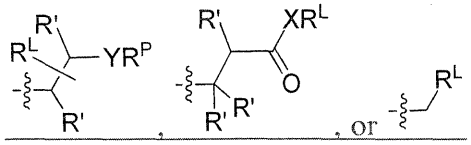
wherein:

p is an integer of between 1 and 9, inclusive;

each instance of R^2 is independently hydrogen or optionally substituted C_{1-6} alkyl;

each instance of R^6 and R^7 is independently a group of the formula (i), (ii), or (iii);

Formulae (i), (ii), and (iii) are:



(i) (ii) (iii)

wherein:

each instance of R' is independently hydrogen or optionally substituted alkyl;

X is O, S, or NR^X, wherein R^X is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

Y is O, S, or NR^Y, wherein R^Y is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl,

optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

R^P is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, or a nitrogen protecting group when attached to a nitrogen atom; and

R^L is optionally substituted C_{1-50} alkyl, optionally substituted C_{2-50} alkenyl, optionally substituted C_{2-50} alkynyl, optionally substituted heteroC_{1-50} alkyl, optionally substituted heteroC_{2-50} alkenyl, optionally substituted heteroC_{2-50} alkynyl, or a polymer, in the manufacture of a medicament for treating a disease or disorder wherein the medicament is to be administered to a subject in need of treatment such that the administering of the medicament results in the expression of the protein encoded by the mRNA in one or more tissues affected by the disease or disorder.

[0008] In some embodiments, a suitable cationic lipid is cKK-E12:

30. The method of any one of claims 1-28, wherein the mRNA is administered at a dose of or less than about 1.0 mg /kg body weight.

31. The method of any one of claims 1-28, wherein the mRNA is administered at a dose of or less than about 0.5 mg /kg body weight.

32. The method of any one of claims 1-28, wherein the mRNA is administered at a dose of or less than about 0.3 mg/kg body weight.

33. The method of any one of the preceding claims, wherein the mRNA comprises one or more modified nucleotides.

34. The method of claim 33, wherein the one or more modified nucleotides comprise pseudouridine, N-1-methyl-pseudouridine, 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3-methyl adenosine, 5-methylcytidine, C-5 propynyl-cytidine, C-5 propynyl-uridine, 2-aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5-propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, O(6)-methylguanine, and/or 2-thiocytidine.

35. The method of any one of claims 1-32, wherein the mRNA is unmodified.

36. ~~A method of treating a disease or disorder comprising~~

~~administering to subject in need of treatment~~ Use of a composition comprising an mRNA encoding a therapeutic protein encapsulated within a liposome ~~such that the administering of the composition results in the expression of the protein encoded by the mRNA in one or more tissues affected by the disease or disorder;~~

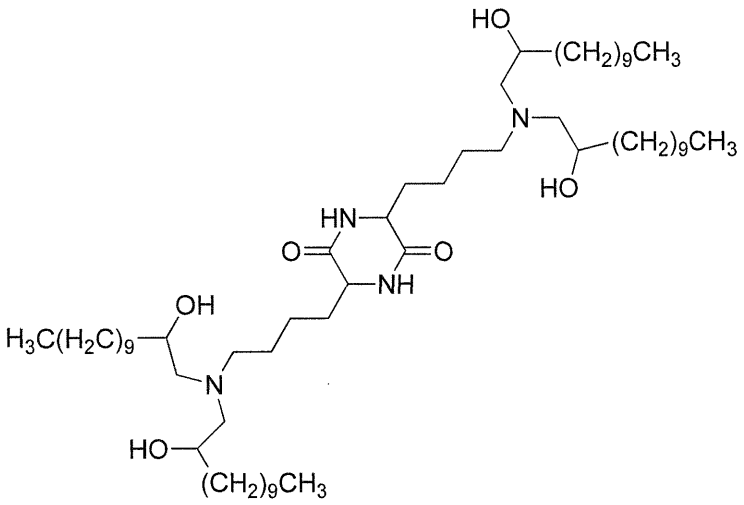
wherein the liposome comprises a cationic lipid of formula I-c:

optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

R^P is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, or a nitrogen protecting group when attached to a nitrogen atom; and

R^L is optionally substituted C_{1-50} alkyl, optionally substituted C_{2-50} alkenyl, optionally substituted C_{2-50} alkynyl, optionally substituted heteroC_{1-50} alkyl, optionally substituted heteroC_{2-50} alkenyl, optionally substituted heteroC_{2-50} alkynyl, or a polymer, in the manufacture of a medicament for treating a disease or disorder wherein the medicament is to be administered to a subject in need of treatment such that the administering of the medicament results in the expression of the protein encoded by the mRNA in one or more tissues affected by the disease or disorder.

37. The ~~method~~ use of claim 36, wherein the cationic lipid is cKK-E12:



38. A composition for delivery of messenger RNA (mRNA) comprising an mRNA encoding a protein encapsulated within a liposome, wherein the liposome comprises a cationic lipid of formula I-c: