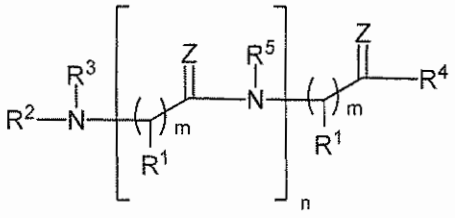
the clinical use of siRNA continues to require development of safer and more effective delivery systems. Toward this end, numerous lipid-like molecules have been developed including poly β-amino esters and amino alcohol lipids. See, *e.g.*, PCT Application Publication Nos. WO 2002/031025; WO 2004/106411; WO 2008/011561; WO 2007/143659; WO 2006/138380; and WO 2010/053572. Amino acid, peptide, polypeptide-lipids (APPL) have also been studied for a variety of applications, including use as therapeutics, biosurfactants, and nucleotide delivery systems. See, *e.g.*, Giuliani *et al., Cellular and Molecular Life Sciences* (2011) 68:2255-2266; Ikeda *et al., Current Medicinal Chemistry* (2007) 14: 111263-1275; Sen, *Advances in Experimental Medicine and Biology* (2010) 672:316-323; and Damen *et al., Journal of Controlled Release* (2010) 145:33-39. However, there continues to remain a need to investigate and develop new APPL systems with improved properties, such as new and improved APPL nucleotide delivery systems.

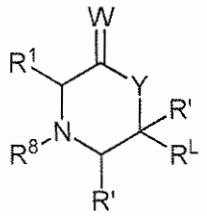
Summary of the Invention

[0005] Described herein are inventive compounds and compositions characterized, in certain embodiments, by conjugation of various groups, such as lipophilic groups, to an amino or amide group of an amino acid, a linear or cyclic peptide, a linear or cyclic polypeptide, or structural isomer thereof, to provide compounds of the present invention, collectively referred to herein as "APPLs". Such APPLs are deemed useful for a variety of applications, such as, for example, improved nucleotide delivery. The subject matter is as defined in the independent claims 1, 14, 36, 52, 60, 78, 80, and 82, and their dependent claims.

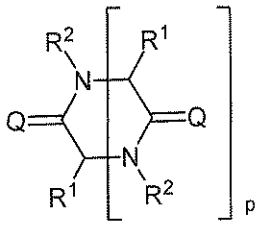
[0006] Exemplary APPLs include, but are not limited to, compounds of Formula (I), (II), (III), (IV), (V), and (VI), and salts thereof, as described herein:



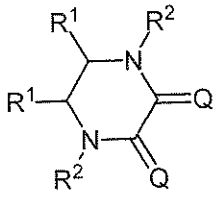
(I)



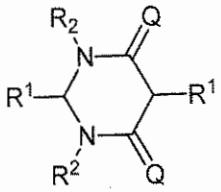
(II)



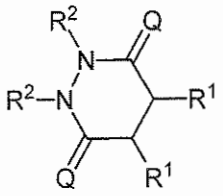
(III)



(IV)

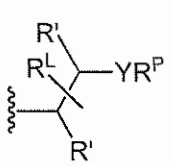


(V)

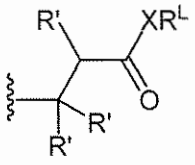


(VI)

wherein m, n, p, R′, R^1, R^2, R^3, R^4, R^5, R^8, Z, W, Y, and Z are as defined herein, provided that the APPL comprises at least one instance of a group of formula (i), (ii), or (iii):

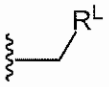


(i)



(ii)

or



(iii)

wherein:

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

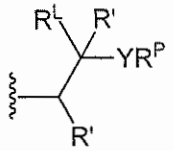
X is O, S, NR^X, wherein R^X is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

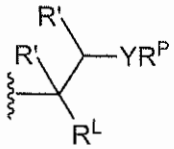
Y is O, S, NR^Y, wherein R^Y is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

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

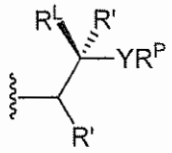
R^L is optionally substituted C_{1-50} alkyl, optionally substituted C_{2-50} alkenyl, optionally substituted C_{2-50} alkynyl, optionally substituted heteroC_{1-50} alkyl, optionally substituted heteroC_{2-50} alkenyl, optionally substituted heteroC_{2-50} alkynyl, or a polymer.

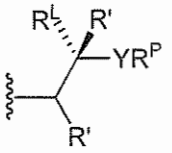
[0007] In certain ~~embodiments~~examples, the group of formula (i) represents a group of formula (i-a) or a group of formula (i-b):


(i-a)

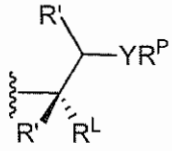

(i-b).

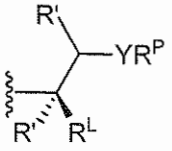
[0008] In certain ~~embodiments~~examples, the group of formula (i-a) is a group of formula (i-a1) or a group of formula (i-a2):


(i-a1)

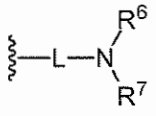

(i-a2).

[0009] In certain ~~embodiments~~examples, the group of formula (i-b) is a group of formula (i-b1) or a group of formula (i-b2):


(i-b1)


(i-b2)

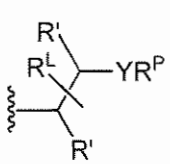
[0010] In certain ~~embodiments~~examples, at least one instance of R^1 is a group of formula:

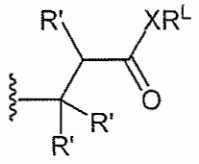

(iv)

wherein L is an optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, optionally substituted arylene, or optionally substituted heteroarylene, and

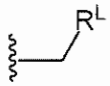
R^6 and R^7 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group;

provided at least one instance of R^6 and R^7 is a group of formula:


(i)


(ii)

or


(iii)

wherein:

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

X is O, S, 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, 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;

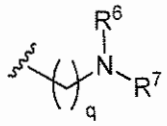
R^P is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen 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.

[0011] In certain ~~embodiments~~examples, each instance of R′ is hydrogen.

[0012] In certain ~~embodiments~~examples, L is an optionally substituted alkylene.

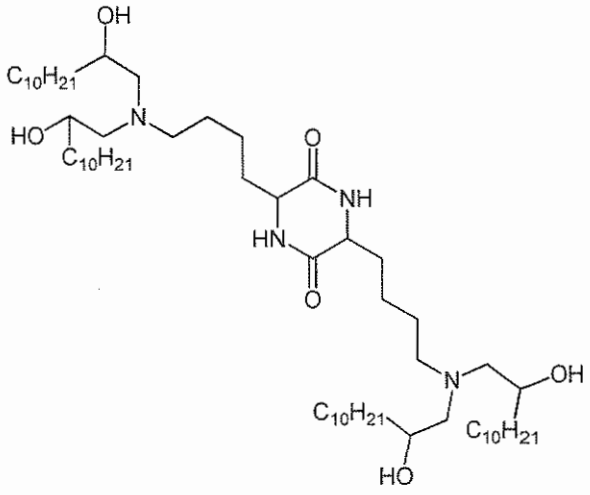
[0013] In certain ~~embodiments~~examples, the group of formula (iv) is of formula:



wherein q is an integer between 1 and 50, inclusive.

[0014] In certain ~~embodiments~~examples, each instance of R^1 is a group of formula (iv).

[0015] An exemplary APPL of the present invention is compound (**cKK-E12**):



(**cKK-E12**),

or a salt thereof.

[0016] In another ~~aspect~~example, provided are compositions comprising an APPL or a salt thereof.

[0017] ~~For example, l~~In certain ~~embodiments~~examples, provided is a composition comprising an APPL or salt thereof and, optionally, an excipient, wherein the APPL is an amino acid, a linear or cyclic peptide, a linear or cyclic polypeptide, or structural isomer thereof, and wherein an amino or amide group of the APPL is conjugated to a group of formula (i), (ii), or (iii). In certain ~~embodiments~~examples, the group of formula (i), (ii), or (iii) is attached to an amino group present on the APPL scaffold. In certain ~~embodiments~~examples, the composition is a pharmaceutical composition, a cosmetic composition, a nutraceutical composition, or a composition with non-medical application. In certain ~~embodiments~~examples, the composition with non-medical application is an emulsion or emulsifier useful as a food component, for extinguishing fires, for disinfecting surfaces, or for oil cleanup.

[0018] In certain ~~embodiments~~examples, the composition further comprises an agent. In certain ~~embodiments~~examples, the agent is an organic molecule, inorganic molecule, nucleic acid, protein, peptide, polynucleotide, targeting agent, an isotopically labeled chemical compound, vaccine, an immunological agent, or an agent useful bioprocessing, *e.g.*, in the intracellular manufacturing of proteins. In certain ~~embodiments~~examples, the agent is a polynucleotide, and the polynucleotide is DNA or RNA. In certain ~~embodiments~~examples, the RNA is RNA*i*, dsRNA, siRNA, shRNA, miRNA, or antisense RNA. In certain ~~embodiments~~examples, the agent and the APPL are not covalently attached, *e.g.*, for example, the agent and the APPL are non-covalently complexed to each other. However, in certain ~~embodiments~~examples, the agent and the APPL are covalently attached.

[0019] In certain ~~embodiments~~examples, the composition is in the form of a particle. In certain embodiments, the particle is a nanoparticle or microparticle. In certain ~~embodiments~~examples, the particle is a micelle, liposome, or lipoplex. In certain ~~embodiments~~examples, the particle encapsulates an agent, *e.g.*, an agent to be delivered.

[0020] In another ~~aspect~~example, provided is a method of delivering a polynucleotide to a biological cell, comprising providing a composition comprising an APPL, or salt thereof, and a polynucleotide, and exposing the composition to the biological cell under conditions sufficient to facilitate delivery of the polynucleotide into the interior of the biological cell; wherein the APPL is an amino acid, a linear or cyclic peptide, or a linear or cyclic polypeptide, or structural isomer thereof, wherein an amino or amide group of the APPL is conjugated to a group of formula (i), (ii), or (iii). In certain ~~embodiments~~examples, the polynucleotide is DNA or RNA. In certain ~~embodiments~~examples, the RNA is RNA*i*, dsRNA, siRNA, shRNA, miRNA, or antisense RNA. In certain ~~embodiments~~examples, upon delivery of the RNA into the cell, the RNA is able to interfere with the expression of a specific gene in the biological cell.

[0021] In yet another ~~aspect~~example, provided are screening methods. For example, in one ~~embodiment~~example, provided is a method of screening a compound library, the method comprising providing a plurality of different APPLs, or salts thereof, and performing at least one assay with the compound library to determine the presense or absence of a desired property; wherein the APPL is an amino acid, a linear or cyclic peptide, or a linear or cyclic polypeptide, or structural isomer thereof, wherein an amino or amide group of the APPL is conjugated to a group of formula (i), (ii), or (iii). In certain ~~embodiments~~examples, the desired property is solubility in water, solubility at different pH, ability to bind polynucleotides, ability to bind heparin, ability to bind small molecules, ability to bind protein, ability to form microparticles, ability to increase tranfection efficiency, ability to support cell growth, ability to support cell attachment, ability to support tissue growth, and/or intracellular delivery of the APPL and/or an agent complexed or attached thereto to aid in bioprocessing.

[0022] In still yet another ~~aspect~~example, provided are methods of use of the inventive APPLs for the treatment of various diseases, disorders, or conditions. ~~For example, I~~in certain ~~embodiments~~examples, provided is a method of treating a disease, disorder, or condition from which the subject suffers, comprising administering to a subject in need thereof an effective amount of an APPL, or salt thereof, wherein the APPL is an amino acid, a linear or cyclic peptide, or a linear or cyclic polypeptide, or structural isomer thereof,

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

Y is O, S, 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;

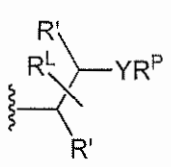
R^P is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen 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.

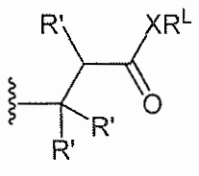
79. The method of claim 78, wherein the desired property is solubility in water, solubility at different pH, ability to bind polynucleotides, ability to bind heparin, ability to bind small molecules, ability to bind protein, ability to form microparticles, ability to increase tranfection efficiency, ability to support cell growth, ability to support cell attachment, ability to support tissue growth, and/or intracellular delivery of the APPL and/or an agent complexed or attached thereto to aid in bioprocessing.

80. ~~A method of~~Use of a composition comprising an APPL, or salt thereof for treating disease, disorder, or condition from which a subject suffers~~, comprising administering to a subject in need thereof an effective amount of a composition comprising an APPL, or salt thereof~~;

wherein the APPL is an amino acid, a linear or cyclic peptide, or a linear or cyclic polypeptide, or structural isomer thereof, wherein an amino or amide group of the APPL is conjugated to a group of formula (i), (ii), or (iii):

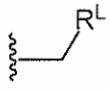


(i)



(ii)

or



(iii)

wherein:

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

X is O, S, 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, 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;~~.~~

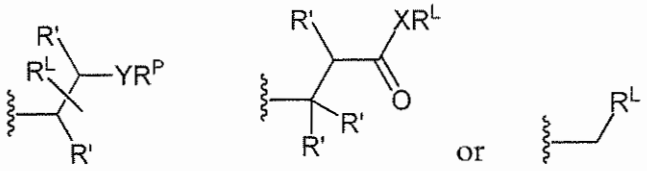
~~81. The method of claim 80,~~ wherein the disease, disorder, or condition is selected from the group consisting of proliferative disorders, inflammatory disorders, autoimmune disorders, painful conditions, liver diseases, and familial amyloid neuropathies.

~~82.~~81. An in vitro method of delivering a polynucleotide to a biological cell, comprising:

providing a composition comprising an APPL, or salt thereof, and a polynucleotide; and

exposing the composition to the biological cell under conditions sufficient to facilitate delivery of the polynucleotide into the interior of the biological cell;

wherein the APPL is an amino acid, a linear or cyclic peptide, or a linear or cyclic polypeptide, or structural isomer thereof, wherein an amino or amide group of the APPL is conjugated to a group of formula (i), (ii), or (iii):



(i) (ii) (iii)

wherein:

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

X is O, S, 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, 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.

~~83.~~82. The method of claim 81~~82~~, wherein the polynucleotide is DNA or RNA.

~~84.~~83. The method of claim ~~83~~82, wherein the RNA is RNA*i*, dsRNA, siRNA, shRNA, miRNA, or antisense RNA.

~~85.~~84. The method of claim ~~84~~83, wherein upon delivery of the RNA into the cell, the RNA is able to interfere with the expression of a specific gene in the biological cell.