bPEI-25 to interact electrostatically with negative charged nucleic acids over a broad pH range and to complex them into nanoparticles. Once bPEI-25/nucleic acid nanocomplexes are internalized by the cells, the secondary and tertiary amines facilitate the release of the nucleic acids from the endosomes through the "proton sponge effect". In the case of deoxyribonucleic acid (DNA), the uptake of the released nucleic acids into the nucleus confers high gene transfer efficiency.

[0005] Despite its high gene transfection efficiency, the net positive charge of bPEI-25 has major drawbacks concerning toxicity, aggregation and undesired non-specific interactions of bPEI-25/nucleic acid complexes with cellular and non-cellular components, particular in vivo. Adverse effects include liver necrosis, adhesion of aggregated platelets and shock after systemic injection of higher doses.

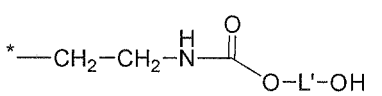
[0006] In view of the cytotoxic issues faced by bPEI-25, a low molecular weight branched polyethylenimine (Mw about 2.0 kDa, Mn about 1.8 kDa, referred to herein as bPEI-2) has gained interest as well due to its favorable cytotoxicity profile. Low molecular weight enables bPEI-2 to be excreted from the kidneys when used for in vivo therapeutic purposes. However, the major disadvantage of bPEI-2 is its inefficient transfection ability rendering it inadequate for use as a gene transfection vector.

[0007] Thus, an ongoing need exists to develop more efficient and less cytotoxic polyethylenimine derivatives for delivery of biologically active materials.

SUMMARY

[0008] ~~In a first aspect of the present disclosure, there~~ There is provided~~,~~ a branched polyamine~~,~~ comprising:

about 8 to about 12 backbone tertiary amine groups, about 18 to about 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to about 8 to about 12,

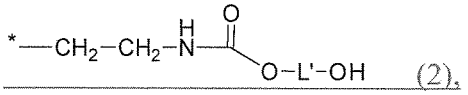
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

q/(n' + q) × 100% equals about 9% to about 40%.

[0008a] In a first aspect, there is provided a branched polyamine, comprising:

8 to 12 backbone tertiary amine groups, 18 to 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to 8 to 12,

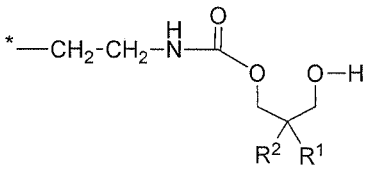
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

q/(n' + q) × 100% equals 9% to 40%.

[0009] ~~In a second aspect, there~~ There is also provided a branched polyamine, comprising:

about 8 to about 12 backbone tertiary amine groups, about 18 to about 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (4):



(4),

wherein

the starred bond of formula (4) is linked to a backbone nitrogen of the branched polyamine,

R^1 is hydrogen, methyl, or ethyl,

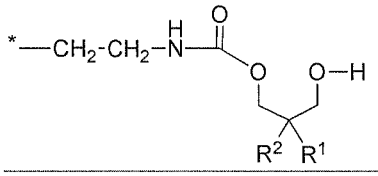
R^2 is hydrogen or a monovalent radical comprising 1 to 27 carbons,

(n'+q) is a number equal to about 8 to about 12, and

q/(n' + q) × 100% equals about 9% to about 40%.

[0009a] In a second aspect, there is provided a branched polyamine, comprising:

8 to 12 backbone tertiary amine groups, 18 to 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (4):



(4),

wherein

the starred bond of formula (4) is linked to a backbone nitrogen of the branched polyamine,

R^1 is hydrogen, methyl, or ethyl,

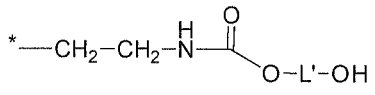
R^2 is hydrogen or a monovalent radical comprising 1 to 27 carbons,

(n'+q) is a number equal to 8 to 12, and

q/(n' + q) × 100% equals 9% to 40%.

[0010] ~~In a third aspect, there~~There is also provided a method, comprising:

treating a branched first polymer comprising about 8 to about 12 primary amine groups, a plurality of secondary amine groups, and a plurality of tertiary amine groups with a cyclic carbonate monomer without polymerizing the cyclic carbonate monomer, thereby forming a branched polyamine comprising i) about 8 to about 12 backbone tertiary amine groups, ii) about 18 to about 24 backbone secondary amine groups, iii) a positive number n' greater than 0 of backbone terminating primary amine groups, and iv) a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to about 8 to about 12,

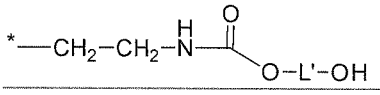
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

q/(n' + q) × 100% equals about 9% to about 40%.

[0010a] In a third aspect, there is provided a method, comprising:

treating a branched first polymer comprising 8 to 12 primary amine groups, a plurality of secondary amine groups, and a plurality of tertiary amine groups with a cyclic carbonate monomer without polymerizing the cyclic carbonate monomer, thereby forming a branched polyamine comprising i) 8 to 12 backbone tertiary amine groups, ii) 18 to 24 backbone secondary amine groups, iii) a positive number n' greater than 0 of backbone terminating primary amine groups, and iv) a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to 8 to 12,

the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

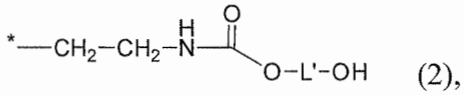
q/(n' + q) × 100% equals 9% to 40%.

[0011] ~~In a fourth aspect there~~There is also provided a complex, comprising:

a gene; and

a branched polyamine comprising about 8 to about 12 backbone tertiary amine groups, about 18 to about 24 backbone secondary amine groups, a positive number n' greater than 0

of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to about 8 to about 12,

the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

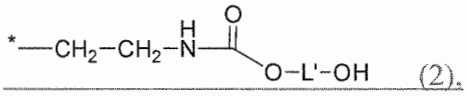
L' is a divalent linking group comprising 3 to 30 carbons, and

q/(n' + q) × 100% equals about 9% to about 40%.

[0011a] In a fourth aspect there is provided a complex, comprising:

a gene; and

a branched polyamine comprising 8 to 12 backbone tertiary amine groups, 18 to 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to 8 to 12,

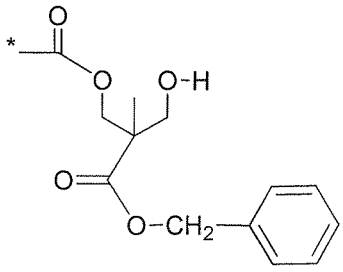
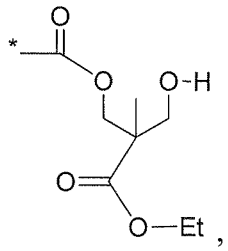
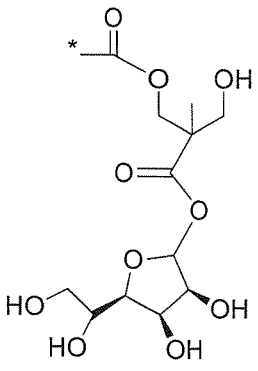
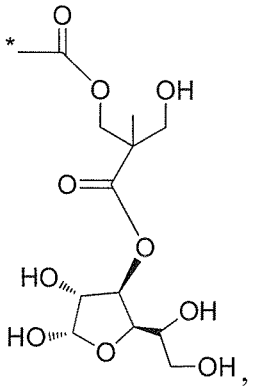
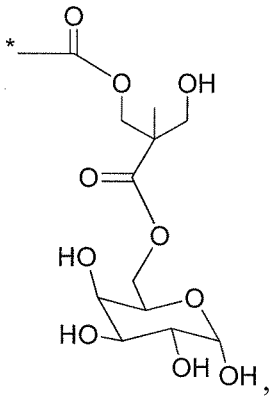
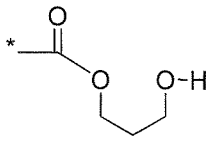
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

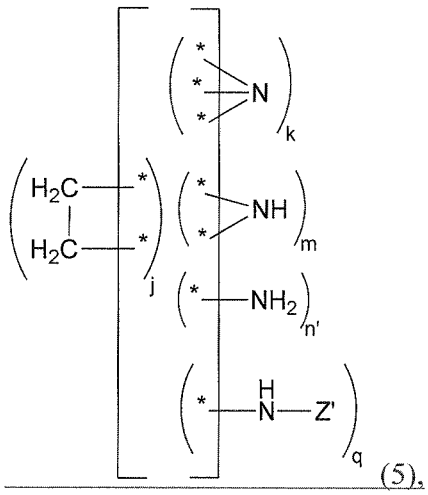
q/(n' + q) × 100% equals 9% to 40%.

[0012] In a fifth aspect, there is provided use of the complex as disclosed above in the manufacture of a medicament for the treatment of cancer, wherein the complex is contacted with a cell.

[0013] ~~In a sixth aspect there~~ There is also provided a branched polyamine having a structure according to formula (5):

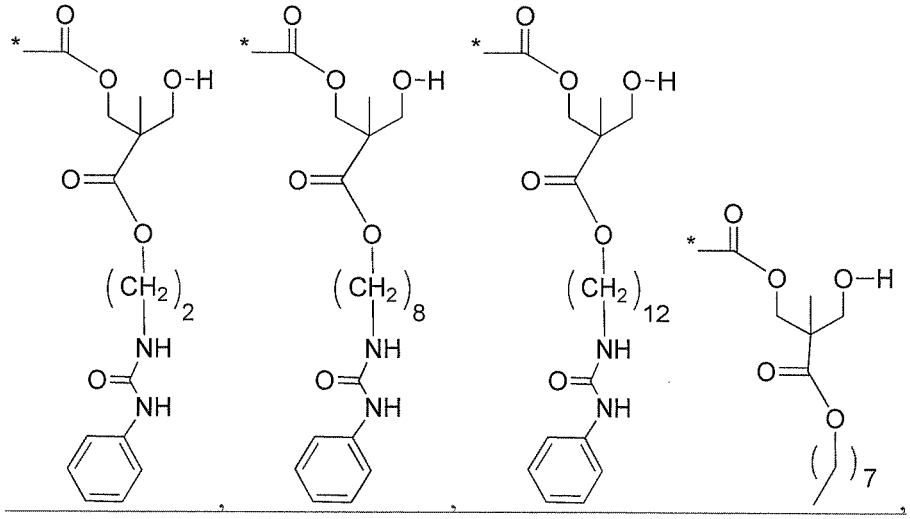






, and combinations thereof.

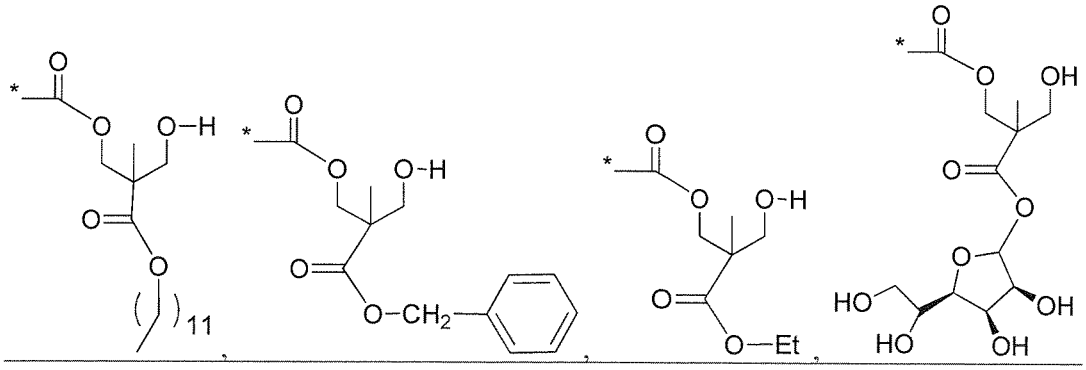
[0013a] In a sixth aspect, there is provided a branched polyamine having a structure according to formula (5):

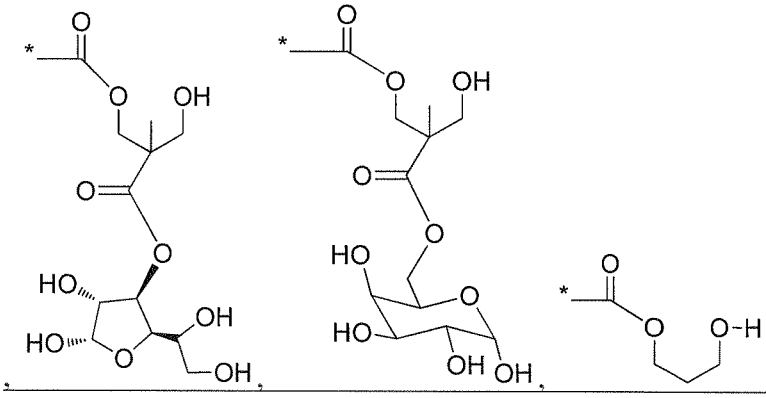

(5),

wherein j, k, m, n' and q represent molar amounts greater than 0, j has a value 35 to 47, k has a value of 8 to 12, m has a value of 18 to 24, (n'+q) has a value of 8 to 12, and q/(n' + q) ×

100% has a value of 9% to 40%, and each Z' is an independent moiety selected from the group consisting of







, and combinations thereof.

[0014] The above-described and other features and advantages of the present disclosure will be appreciated and understood by those skilled in the art from the following detailed description, drawings, and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 is a bar graph showing particle sizes of polymer/DNA complexes prepared with luciferase reporter gene and various modified bPEI-2 polymers. Non-modified bPEI-2 is a branched polyethylenimine having a number average molecular weight (Mn) = 1.8 kDa, and a weight average molecular weight (Mw) = 2000. The cyclic carbonate monomer used to form the modified bPEI-2 polymer is shown in parentheses in the legend. The complexes were prepared at N/P ratios of 10 to 40. A luciferase reporter gene complex of non-modified bPEI-2 was prepared at N/P ratio of 40 as a control.

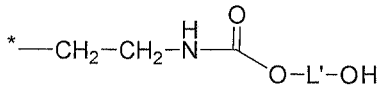
[0016] Figure 2 is a bar graph showing zeta potentials of polymer/DNA complexes prepared with luciferase reporter gene and various modified bPEI-2 polymers. The cyclic

CLAIMS

What is claimed is:

1. A branched polyamine, comprising:

~~about~~ 8 to ~~about~~ 12 backbone tertiary amine groups, ~~about~~ 18 to ~~about~~ 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to ~~about~~ 8 to ~~about~~ 12,

the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

q/(n' + q) × 100% equals ~~about~~ 9% to ~~about~~ 40%.

2. The branched polyamine of claim 1, wherein the branched polyamine consists ~~essentially~~ of n' primary ethylenimine repeat units, ~~about~~ 18 to ~~about~~ 24 secondary ethylenimine repeat units, ~~about~~ 8 to ~~about~~ 12 tertiary ethylenimine repeat units, and q carbamate groups of formula (2).

3. The branched polyamine of claim 1, wherein the branched polyamine is a carbamate functionalized branched polyethylenimine having a number average molecular weight of ~~about~~ 1600 to ~~about~~ 5000.

4. The branched polyamine of claim 1, wherein a gene complex of the branched polyamine is non-cytotoxic at N/P 10 to N/P 50.

5. The branched polyamine of claim 1, wherein L' comprises a phenyl urea moiety.

6. The branched polyamine of claim 1, wherein q/(n' + q) × 100% equals ~~about~~ 9% to

~~about~~ 25%.

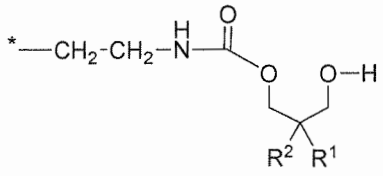
7. The branched polyamine of claim 1, wherein q/(n' + q) × 100% equals ~~about~~ 9% to ~~about~~ 12%.

8. The branched polyamine of claim 1, wherein the carbamate groups are not charged.

9. The branched polyamine of claim 1, wherein the branched polyamine has no quaternary amine groups.

10. A branched polyamine, comprising:

~~about~~ 8 to ~~about~~ 12 backbone tertiary amine groups, ~~about~~ 18 to ~~about~~ 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (4):



(4),

wherein

the starred bond of formula (4) is linked to a backbone nitrogen of the branched polyamine,

R^1 is hydrogen, methyl, or ethyl,

R^2 is hydrogen or a monovalent radical comprising 1 to 27 carbons,

(n'+q) is a number equal to ~~about~~ 8 to ~~about~~ 12, and

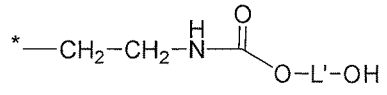
q/(n' + q) × 100% equals ~~about~~ 9% to ~~about~~ 40%.

11. The branched polyamine of claim 10, wherein R^2 is an ester *-C(=O)OR^3, wherein R^3 comprises 1 to 26 carbons.

12. A method, comprising:

treating a branched first polymer comprising ~~about~~ 8 to ~~about~~ 12 primary amine groups, a plurality of secondary amine groups, and a plurality of tertiary amine groups with a cyclic carbonate monomer without polymerizing the cyclic carbonate monomer,

thereby forming a branched polyamine comprising i) ~~about~~ 8 to ~~about~~ 12 backbone tertiary amine groups, ii) ~~about~~ 18 to ~~about~~ 24 backbone secondary amine groups, iii) a positive number n' greater than 0 of backbone terminating primary amine groups, and iv) a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to ~~about~~ 8 to ~~about~~ 12,

the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

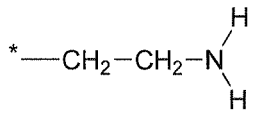
q/(n' + q) × 100% equals ~~about~~ 9% to ~~about~~ 40%.

13. The method of claim 12, wherein the cyclic carbonate monomer comprises one or more protecting groups, and the method further comprises selectively removing the one or more protecting groups from the branched polyamine.

14. The method of claim 12, wherein the cyclic carbonate is a 6-membered ring cyclic carbonate.

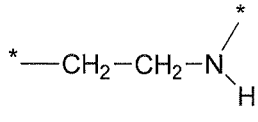
15. The method of claim 12, wherein the branched first polymer is a branched polyethylenimine having a backbone consisting essentially of:

~~about~~ 25 mol% primary ethylenimine repeat units having a structure



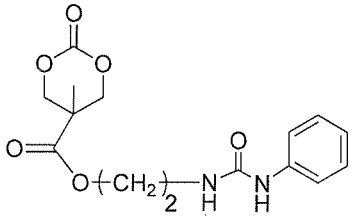
,

~~about~~ 50 mol% secondary ethylenimine repeat units having a structure

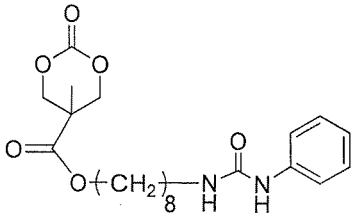


, and

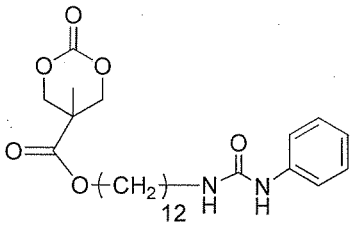
~~about~~ 25 mol% tertiary ethylenimine repeat units having a structure



(MTC-PUC2),



(MTC-PUC8),

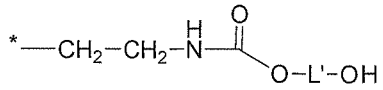


(MTC-PUC12), and combinations thereof.

17. A complex, comprising:

a gene; and

a branched polyamine comprising ~~about~~ 8 to ~~about~~ 12 backbone tertiary amine groups, ~~about~~ 18 to ~~about~~ 24 backbone secondary amine groups, a positive number n' greater than 0 of backbone terminating primary amine groups, and a positive number q greater than 0 of backbone terminating carbamate groups of formula (2):



(2),

wherein:

(n'+q) is a number equal to ~~about~~ 8 to ~~about~~ 12,

the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

L' is a divalent linking group comprising 3 to 30 carbons, and

q/(n' + q) × 100% equals ~~about~~ 9% to ~~about~~ 40%.

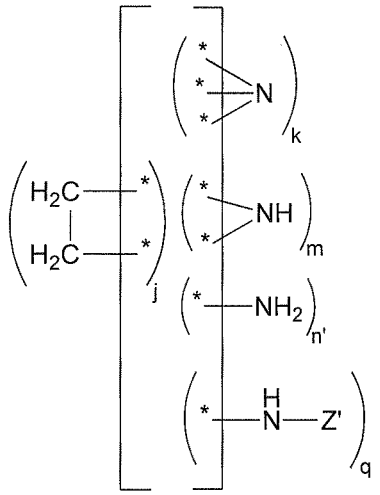
18. Use of a complex of claim 17 in the manufacture of a medicament for the treatment of cancer, wherein the complex is contacted with a cell.

19. The use of claim 18, wherein the cell is a human tumor cell.

20. The use of claim 18, wherein the cell is a cancerous liver cell.

21. The use of claim 18, wherein the cell is a cancerous ovarian cell.

22. A branched polyamine having a structure according to formula (5):



(5),

wherein j, k, m, n' and q represent molar amounts greater than 0, j has a value ~~about~~ 35 to ~~about~~ 47, k has a value of ~~about~~ 8 to ~~about~~ 12, m has a value of ~~about~~ 18 to ~~about~~ 24, (n'+q) has a value of ~~about~~ 8 to ~~about~~ 12, and q/(n' + q) × 100% has a value of ~~about~~ 9% to ~~about~~ 40%, and each Z' is an independent moiety selected from the group consisting of

