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.

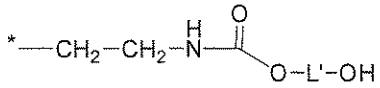
[0006] In view of the cytotoxic issues faced by bPEI-25, a low molecular weight branched polyethylenimine (Mw about 2.0 kDa, Mn about 1.8 kDa, referred to herein as bPEI-2) has gained interest as well due to its favorable cytotoxicity profile. Low molecular weight enables bPEI-2 to be excreted from the 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 is provided ~~Accordingly,~~ a branched polyamine ~~is disclosed~~, 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,

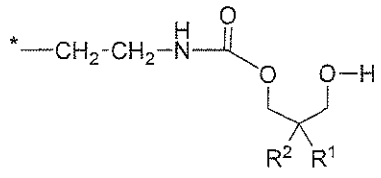
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

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

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

[0009] In a second aspect, there is provided ~~Also disclosed is~~ 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,

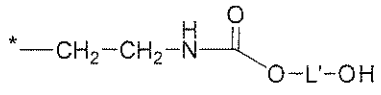
R^2 is hydrogen or a monovalent radical comprising 1 to 27 carbons,

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

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

[0010] In a third aspect, there is provided ~~Further disclosed is~~ 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,

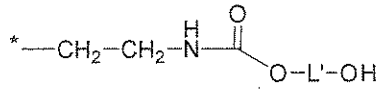
L' is a divalent linking group comprising 3 to 30 carbons, and

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

[0011] In a fourth aspect there is provided~~Also disclosed is~~ 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,

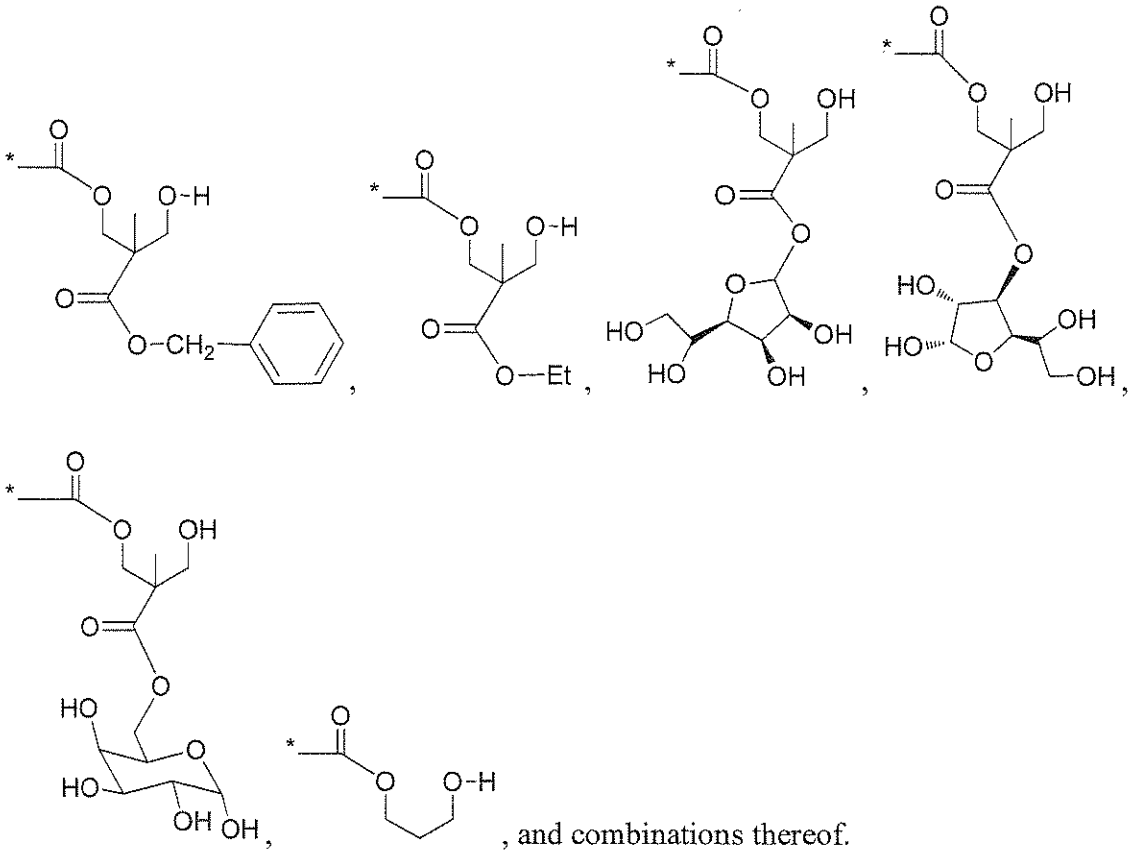
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

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

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

[0012] In a fifth aspect, there is provided~~Also disclosed is~~ 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~~a method of treating a cell, comprising contacting the cell with the above-described complex~~.

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

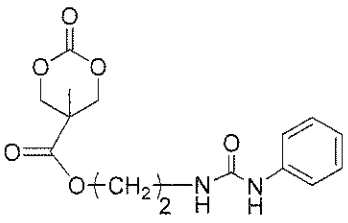


[0014] The above-described and other features and advantages of the present ~~invention~~ disclosure will be appreciated and understood by those skilled in the art from the following detailed description, drawings, and appended claims.

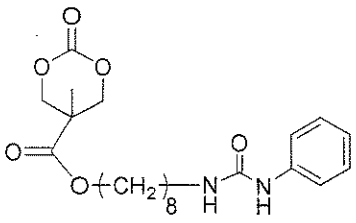
BRIEF DESCRIPTION OF THE DRAWINGS

[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.

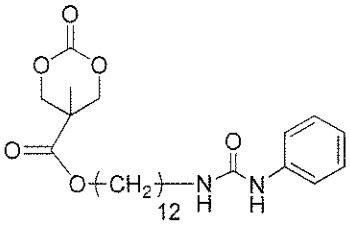
Figure 2 is a bar graph showing zeta potentials of polymer/DNA complexes prepared with luciferase reporter gene and various modified bPEI-2 polymers. The cyclic



(MTC-PUC2),



(MTC-PUC8),

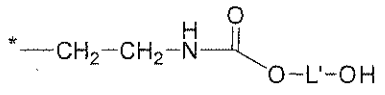


(MTC-PUC12), and combinations thereof.

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%.

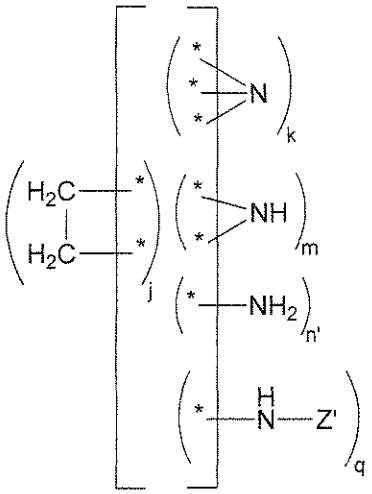
18. Use of ~~A~~ a complex of claim 17 in the manufacture of a medicament~~method of treating a cell, comprising~~ for the treatment of cancer, wherein the complex is contacted with a~~contacting the~~ cell ~~with the complex of claim 17~~.

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

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

21. The ~~use~~method 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

