negatively 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.

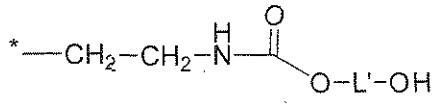
[0006] In view of the cytotoxic issues faced by bPEI-25, low molecular weight branched polyethylenimine (Mw about 2.0 kDa, Mn about 1.8 kDa, referred to herein as bPEI-2) has gained interest as well due to its favorable cytotoxicity profile. Low molecular weight enables bPEI-2 to be excreted from the 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 45 to about 70 backbone tertiary amine groups, about 90 to about 140 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 45 to about 70,

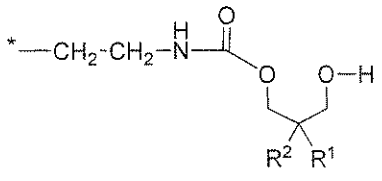
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

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

q/(n' + q) × 100% equals about 9% to about 47%.

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

about 45 to about 70 backbone tertiary amine groups, about 90 to about 140 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 the 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,

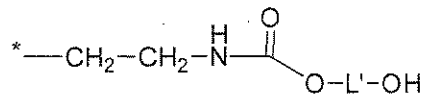
R^2 is hydrogen or a monovalent radical comprising 1 to 27 carbons,

(n'+q) is a number equal to about 45 to about 70, and

q/(n' + q) × 100% equals about 9% to about 47%.

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

treating a branched first polymer comprising about 45 to about 70 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 45 to about 70 backbone tertiary amine groups, ii) about 90 to about 140 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 45 to about 70,

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

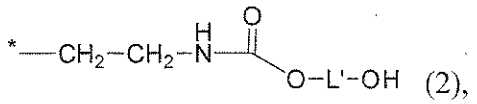
L' is a divalent radical comprising 3 to 30 carbons, and

q/(n' + q) × 100% equals about 9% to about 47%.

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

a gene; and

a branched polyamine comprising about 45 to about 70 backbone tertiary amine groups, about 90 to about 140 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 45 to about 70,

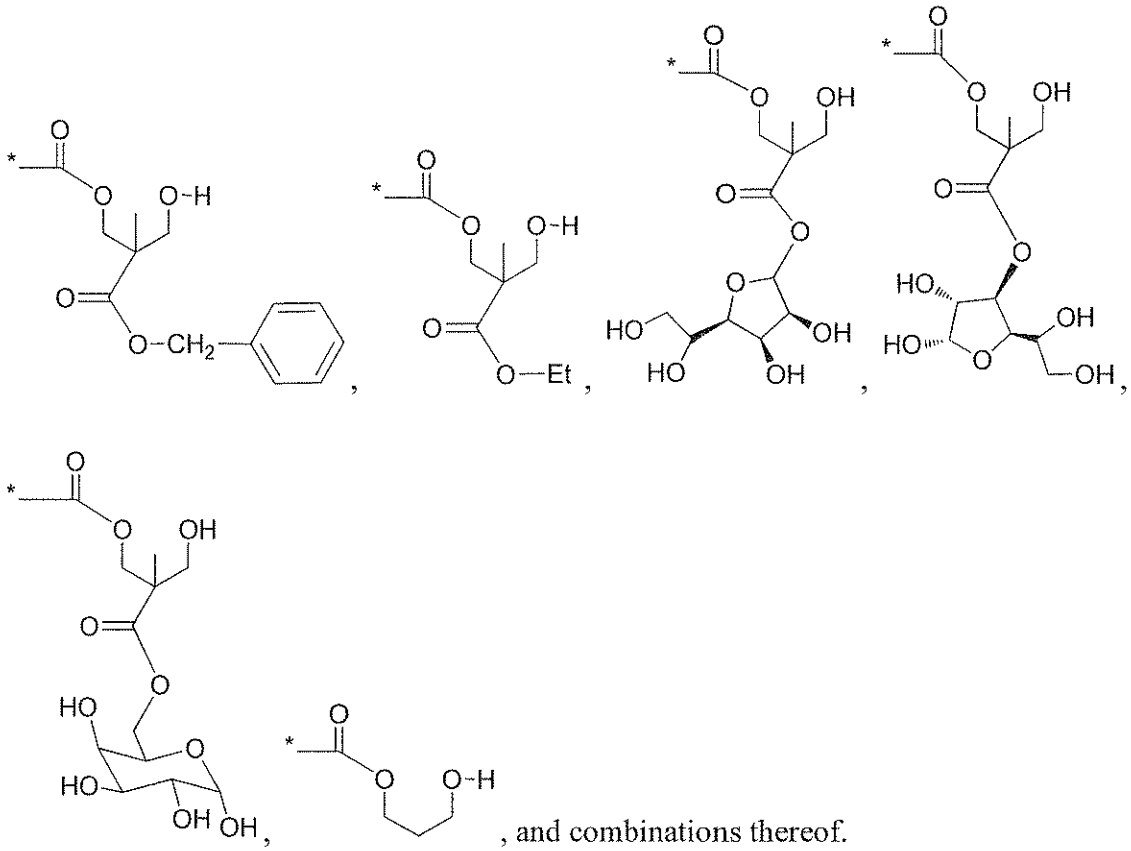
the starred bond of formula (2) is linked to a backbone nitrogen of the branched polyamine,

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

q/(n' + q) × 100% equals about 9% to about 47%.

[0012] In a fifth aspect, there is provided use of the complex as described above in the manufacture of a medicament for the treatment of cancer, wherein the complex is contacted with~~Also disclosed is 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):



, and combinations thereof.

[0014] The above-described and other features and advantages of the present disclosure~~invention~~ 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 green fluorescent protein (GFP) reporter gene complexes prepared with carbamate functionalized branched polyethylenimine polymers **A**, **B**, and **C**. **A**, **B**, and **C** were prepared from a commercially available bPEI-25. The gene complexes were prepared at N/P 5 to 30. "N/P" refers to the molar ratio of nitrogen of the carbamate functionalized bPEI-25 polymer to phosphorus of the gene, and is indicative of the net charge of the carbamate functionalized bPEI-25/gene complex. A control gene complex of bPEI-25 was prepared at N/P 10 (not shown), which had an average particle diameter of about 84 nm and a zeta potential of about 22 mV.

21. Use of ~~A~~ a complex of claim 19 in the manufacture of a medicament ~~method of treating a cell, comprising~~ for the treatment of cancer, wherein the complex is contacted with ~~contacting a the~~ cell ~~with the complex of claim 19~~.

22. The use ~~The method~~ of claim 21, wherein the cell is a human tumor cell.

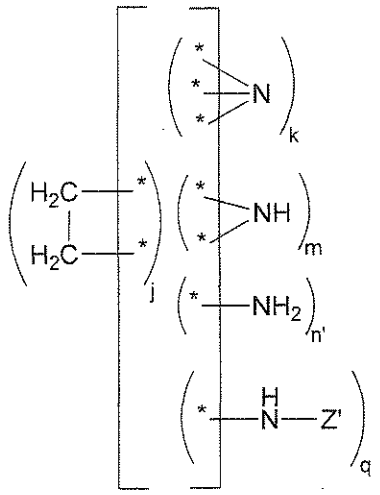
23. The use~~method~~ of claim 21, wherein the cell is a cancerous liver cell.

24. The use~~method~~ of claim 21, wherein the cell is a cancerous cervical cell.

25. The use~~method~~ of claim 21, wherein the cell is a cancerous ovarian cell.

26. The use~~method~~ of claim 21, wherein the cell is a human mesenchymal stem cell.

27. 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 185 to about 280, k has a value of about 45 to about 70, m has a value of about 90 to about 140, (n'+q) has a value of about 45 to about 70, and q/(n' + q) × 100% has a value of about 9% to about 47%, and each Z' is an independent moiety selected from the group consisting of