Claims:

1. ~~An~~ compound for reversibly modifying an amphipathic membrane active polymamine comprising:

   R–A^1A^2-amidobenzyl-carbonate,

   wherein

   R comprises steric stabilizer,

   A^1 is a hydrophobic amino acid, and

   A^2 is a hydrophilic uncharged amino acid linked to A^1 via an amide bond, wherein said hydrophilic uncharged amino acid is uncharged at neutral pH~~a steric stabilizer or targeting ligand covalently linked to a dipeptide-amidobenzyl-carbonate~~.

2. The compound of claim 1 wherein the amidobenzyl is a p-amidobenzyl group.

3. The compound of claim 1 wherein the carbonate is an activated amine reactive carbonate.

4. The compound of claim 1 where R is neutral.

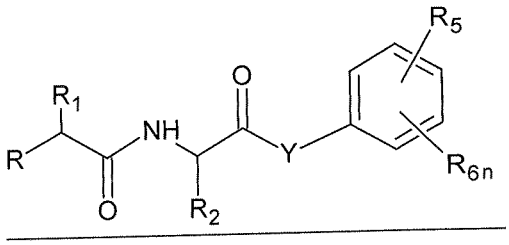
5. The compound of claim 4 where R is uncharged.

6. The compound of claim 1 wherein the steric stabilizer is a polyethylene glycol (PEG).

7. The compound of claim 1 wherein A^1 is selected from the group consisting of: alanine, phenylalanine, valine, leucine, isoleucine, and tryptophan.

8. The compound of claim 1 wherein A^2 is selected from the group consisting of: citrulline, glycine, threonine, dimethyllysine, asparagine, and glutamine.

9. The compound of claim 1 wherein the compound has the structure represented by:



wherein

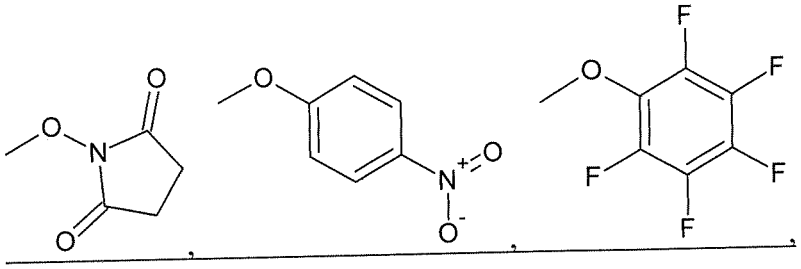
R comprises a steric stabilizer

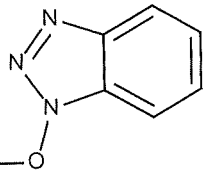
$\mathbf{R^1}$ is a side chain of the hydrophobic amino acid,

$\mathbf{R^2}$ is a side chain of the hydrophilic uncharged amino acid,

–Y– is –NH–, or –O–,

$\mathbf{R^5}$ is at position 2, 4, or 6 and is $-CH_2-O-C(O)-Z$ wherein –Z is





or ; and

$\mathbf{R^6}$ is independently hydrogen, alkyl, $-(CH_2)_m-CH_3$, $-(CH_2)-(CH_3)_2$, or halide at each of positions 2, 3, 4, 5, or 6 except for the position occupied by R^5 and n and m are independently integers from 0 to 4.

10. A delivery polymer for delivering a polynucleotide to a cell *in vivo* comprising:

$$\mathbf{M^1_y–P–M^2_z}$$

wherein:

P is an amphipathic membrane active polyamine,

$\mathbf{M^1}$ comprises a targeting ligand linked to **P** via a dipeptide-amidobenzyl-carbamate linkage,

$\mathbf{M^2}$ comprises a steric stabilizer linked to **P** via a dipeptide-amidobenzyl-carbamate linkage,

y and **z** are each integers greater than or equal to zero,

y + **z** has a value greater than 50% of the primary amines on polyamine **P** as determined by the quantity of amines on **P** in the absence of any masking agents, and the dipeptide-amidobenzyl-carbamate linkage has the structure represented by:

R–$\mathbf{A^1A^2}$-amidobenzyl-carbamate–**P**,

wherein

R comprises the targeting ligand of $\mathbf{M^1}$ or the steric stabilizer of $\mathbf{M^2}$,

$\mathbf{A^1}$ is a hydrophobic amino acid, and

$\mathbf{A^2}$ is a hydrophilic uncharged amino acid linked to A^1 via an amide bond, and

P is the amphipathic membrane active polymer.

11. The delivery polymer of claim 10 wherein the amidobenzyl is a p-amidobenzyl group.

12. The delivery polymer of claim 10 where $\mathbf{M^1}$ and $\mathbf{M^2}$ are independently uncharged or charge neutral.

13. The delivery polymer of claim 10 wherein the steric stabilizer is a PEG.

14. The delivery polymer of claim 10 wherein the targeting ligand comprises cell receptor ligand.

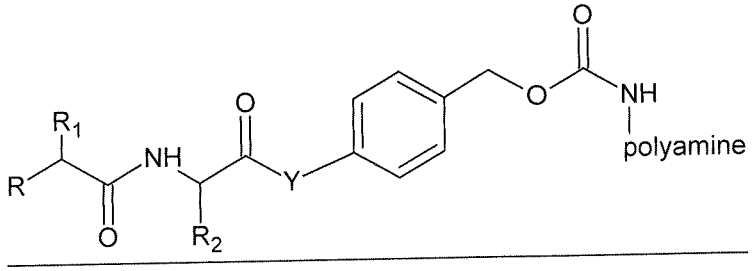
15. The delivery polymer of claim 14 wherein the cell receptor ligand comprises an ASGPr ligand.

16. The delivery polymer of claim 15 wherein the ASGPr ligand is selected from the list consisting of: lactose, galactose, N-acetylgalactosamine, galactosamine, N-formylgalactosamine, N-propionylgalactosamine, N-n-butanoylgalactosamine, and N-iso-butanoyl-galactosamine.

17. The delivery polymer of claim 10 wherein $\mathbf{A^1}$ is selected from the group consisting of: alanine, phenylalanine, valine, leucine, isoleucine, and tryptophan.

18. The delivery polymer of claim 10 wherein $\mathbf{A^2}$ is selected from the group consisting of: citrulline, glycine, threonine, dimethyllysine, asparagine, and glutamine.

19. The delivery polymer of claim 10 wherein **R**–$\mathbf{A^1A^2}$-amidobenzyl-carbamate–**P** has the structure represented by:



wherein

Y is –NH– or –O–,

R1 is a side chain of the hydrophobic amino acid A^1, and

R2 is a side chain of the hydrophilic uncharged amino acid A^2.

20. The delivery polymer of claim 10 wherein the amphipathic membrane active polyamine is selected from the list consisting of: random, block, or alternating synthetic polymer.

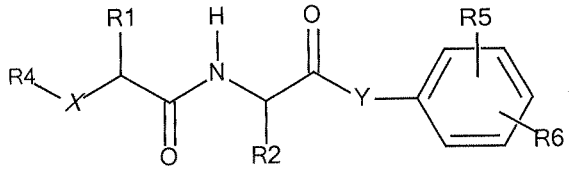
21. The delivery polymer of claim 10 wherein the amphipathic membrane active polyamine is a melittin peptide.

22. The delivery polymer of claim 10 wherein the amphipathic membrane active polyamine is further covalently linked to the polynucleotide.

23. The delivery polymer of claim 22 wherein the polynucleotide comprises an RNA interference polynucleotide.

24. The delivery polymer of claim 23 wherein the RNA interference polynucleotide is selected from the group consisting of: DNA, RNA, dsRNA, siRNA, and miRNA.

225. ~~The~~A compound ~~of claim 1~~for reversibly modifying an amphipathic membrane active polymamine comprising: a targeting ligand covalently linked to a dipeptide-amidobenzyl-carbonate having ~~wherein the compound has~~ the structure represented by:

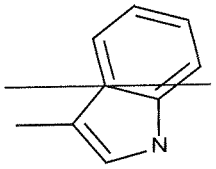


wherein

X is –NH–, ~~–O–, or –CH_2–~~

Y is –NH–, ~~or –O–~~

R1 is ~~–CH_2–phenyl, –CH–$(CH_3)_2$, –CH_2–CH–$(CH_3)_2$, –CH(CH_3)–CH_2–CH_3,~~ –CH_3,



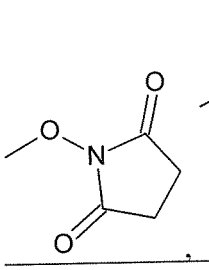
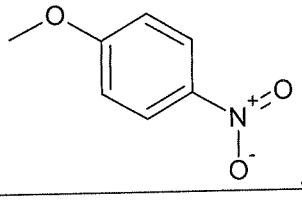
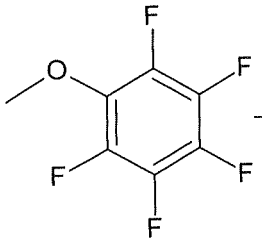
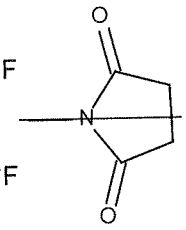
~~or~~ ~~;~~

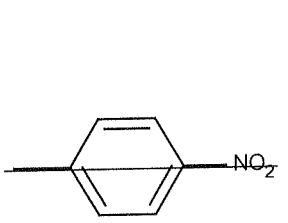
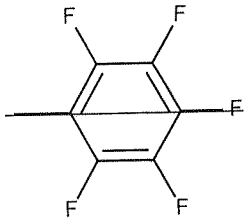
R2 is ~~hydrogen,~~ –$(CH_2)_3$–NH–C(O)–NH_2, ~~–$(CH_2)_4$–N–$(CH_3)_2$, or –CH_2–C(O)–NH_2,~~

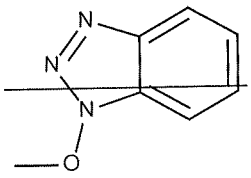
R4 is uncharged and comprises a ~~polyethylene glycol or~~ targeting ligand,

R5 is at position 2, 4, or 6 and is –CH_2–O–C(O)–O–Z wherein Z is

~~–halide,~~



, or


;



~~, or~~


; and

R6 is ~~independently~~ hydrogen~~, alkyl, $-(CH_2)_n-CH_3$ (wherein n = 0-4), $-(CH_2)-(CH_3)_2$, or halide at each of positions 2, 3, 4, 5, or 6 except for the position occupied by R5~~.

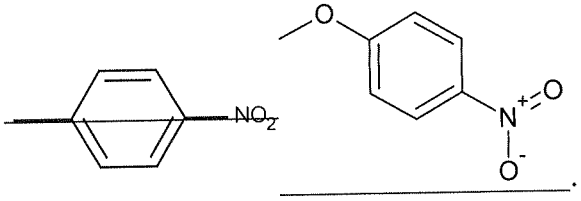
~~3. The compound of claim 2 wherein R4 comprises a steric stabilizer.~~

~~4. The compound of claim 3 wherein the steric stabilizer is a polyethylene glycol (PEG).~~

~~5~~26. The compound of claim ~~2~~25 wherein the targeting ligand comprises an asialoglycoprotein receptor (ASGPr) ligand.

~~6~~27. The compound of claim ~~5~~26 wherein the ASGPr ligand is selected from the list consisting of: lactose, galactose, N-acetylgalactosamine, galactosamine, N-formylgalactosamine, N-propionylgalactosamine, N-n-butanoylgalactosamine, and N-iso-butanoyl-galactosamine.

~~7~~28. The compound of claim ~~1~~25 wherein ~~X and Y are NH-, and~~ Z is


.

8. The compound of claim 7 wherein R1 is $-CH_2-$phenyl.

9. The compound of claim 7 wherein R2 is $-(CH_2)_3-NH-C(O)-NH_2$.

10. A delivery polymer for delivering an RNA interference (RNAi) polynucleotide to a cell *in vivo* comprising:

$\mathbf{M^1}_x\text{-}\mathbf{P}\text{-}\mathbf{M^2}_y$

wherein:

P is an amphipathic membrane active polyamine,

$\mathbf{M^1}$ is a targeting ligand linked to **P** via a dipeptide-amidobenzyl-carbamate linkage,

$\mathbf{M^2}$ is a steric stabilizer linked to **P** via a dipeptide-amidobenzyl-carbamate linkage,

y and **z** are each integers greater than or equal to zero, and

y + **z** has a value greater than 50% of the primary amines on polyamine **P** as determined by the quantity of amines on **P** in the absence of any masking agents.

11. The delivery polymer of claim 10 wherein the steric stabilizer is a PEG.

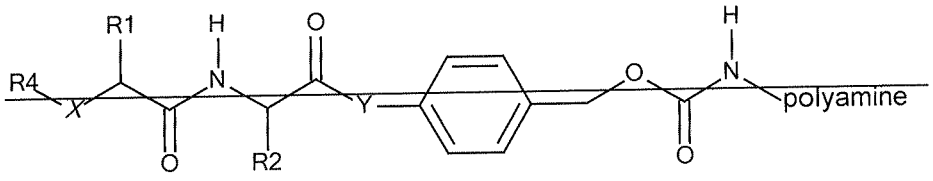
12. The delivery polymer of 10 wherein the targeting ligand comprises an ASGPr ligand.

13. The delivery polymer of claim 12 wherein the ASGPr ligand is selected from the list consisting of: lactose, galactose, N-acetylgalactosamine, galactosamine, N-formylgalactosamine, N-propionylgalactosamine, N-n-butanoylgalactosamine, and N-iso-butanoyl-galactosamine.

14. The delivery polymer of claim 10 wherein the amphipathic membrane active polyamine is selected from the list consisting of: random, block, or alternating synthetic polymer.

15. The delivery polymer of claim 10 wherein the amphipathic membrane active polyamine is a melittin peptide.

16. The delivery polymer of claim 10 wherein the dipeptide-amidobenzyl-carbamate linkage has the structure represented by:

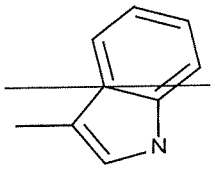


~~wherein~~

~~X is –NH–, –O–, or –CH_2–~~

~~Y is –NH– or –O–~~

~~R1 is –CH_2–phenyl, –CH–$(CH_3)_2$, –CH_2–CH–$(CH_3)_2$, –CH(CH_3)–CH_2–CH_3, –CH_3,~~



~~or~~ ;

~~R2 is hydrogen, –$(CH_2)_3$–NH–C(O)–NH_2, –$(CH_2)_4$–N–$(CH_3)_2$, or –CH_2–C(O)–NH_2,~~

~~R4 comprises the targeting ligand of **M**^{1} or the steric stabilizer of **M**^{2}, and~~

~~polyamine is the amphipathic membrane active polyamine.~~

~~17. The delivery polymer of claim 16 wherein the amphipathic membrane active polyamine is further covalently linked to the RNAi polynucleotide.~~

~~18. A method for delivering an RNAi polynucleotide to a cell in a mammal *in vivo* comprising: co-administering the RNAi polynucleotide with the delivery polymer of claim 10 to the mammal.~~

~~19. The method of claim 18 wherein the RNAi polynucleotide is covalently linked to the delivery polymer.~~

~~20. The method of claim 18 wherein the cell is a hepatocyte or a hepatic cancer cell.~~