CLAIMS

What is claimed is:

1. A composition comprising a lipid-based nanoparticle,

wherein the nanoparticle is enclosed by a bipolar lipid membrane, which comprises cholesterol, dicetyl phosphate, 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), and 2,3-diacetoxypropyl 2-(5-((3aS,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido) ethyl phosphate (biotin DHPE),

wherein the membrane further comprises at least one agent selected from the group consisting of stearoyl lysophosphatidylcholine and m-cresol;

wherein the membrane comprises cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, m-cresol, and biotin DHPE in a % (w/w) ratio selected from the group consisting of:

(a) 9.4 : 18.1 : 56.8 : 14.1 : 0.0 : 1.5;

(b) 7.7 : 15.0 : 58.6 : 0.0 : 17.4 : 1.3; and

(c) 8.4 : 16.2 : 47.5 : 7.6 : 19.0 : 1.3;

wherein the biotin-DHPE extends outward from the nanoparticle; and

wherein the size of the nanoparticle ranges from 10 nm to 150 nm.

2. The composition of claim 1, wherein a therapeutic agent is dispersed within the nanoparticle, and wherein the therapeutic agent comprises at least one selected from the group consisting of insulin, insulin analogs, interferon, parathyroid hormone, calcitonin, serotonin, serotonin agonist, serotonin reuptake inhibitor, human growth hormone, GIP, anti-GIP monoclonal antibody, metformin, bromocriptine, dopamine, glucagon, amylin, and GLP-1.

3. The composition of claim 1, wherein a therapeutic agent is dispersed within the nanoparticle, and further comprising at least one of the following:

(a) cellulose acetate phthalate, which is at least partially bound to the therapeutic agent dispersed within the nanoparticle; and

(b) at least one charged organic molecule associated with the therapeutic agent dispersed within the nanoparticle, wherein the charged organic molecule is at least one selected from the group consisting of protamines, polylysine, poly (arg-pro-thr)$_n$ in a mole ratio of 1:1:1, poly (DL-Ala-poly-L-lys)$_n$ in a mole ratio of 6:1, histones, sugar polymers

comprising a primary amino group, polynucleotides with primary amino groups, proteins comprising amino acid residues with carboxyl (COO^-) or sulfhydral (S^-) functional groups, and acidic polymers.

4. A method of preparing the lipid-based nanoparticle of claim 1, the method comprising: contacting cholesterol, dicetyl phosphate, DSPC, biotin-DHPE, and the at least one agent in an organic solvent-containing system; removing any organic solvent from the system to form a dried material; and suspending and homogenizing the dried material in an aqueous system.

5. The method of claim 4, wherein the at least one agent is m-cresol and is added to the organic solvent-containing system after the cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine if present, and biotin-DHPE had been contacted in the organic solvent-containing system.

6. The method of claim 4, wherein the nanoparticle comprises a therapeutic agent dispersed therewithin, and wherein one of the following applies:

(a) the therapeutic agent, cholesterol, dicetyl phosphate, DSPC, at least one agent, and biotin-DHPE are simultaneously contacted in the organic solvent-containing system; and

(b) the nanoparticle is formed in the absence of the therapeutic agent, wherein the nanoparticle is at least partially concentrated, purified, or isolated, and wherein the therapeutic agent is contacted with the nanoparticle, whereby at least a portion of the therapeutic agent is dispersed within the nanoparticle.

7. A composition comprising a lipid-based nanoparticle,

wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-

phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the membrane comprises at least one agent selected from the group consisting of a stabilizer and stearoyl lysophosphatidylcholine;

wherein the stabilizer is selected from the group consisting of m-cresol, benzyl alcohol, methyl 4-hydroxybenzoate, thiomersal, and butylated hydroxytoluene (2,6-di-*tert*-butyl-4-methylphenol), and wherein, if present, the stabilizer ranges from 10% to 25 % (w/w) in the membrane;

wherein, if present, the stearoyl lysophosphatidylcholine ranges from 1% to 30% (w/w) in the membrane;

wherein the membrane comprises the cholesterol, the dicetyl phosphate, the amphipathic lipid, the at least one agent, and the hepatocyte receptor binding molecule in a % (w/w) ratio such that:

the cholesterol ranges from about 5% to about 15% (w/w),
the dicetyl phosphate ranges from about 10% to about 25% (w/w), and
the hepatocyte receptor binding molecule ranges from about 0.5% to about 4% (w/w);

wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and

wherein the size of the nanoparticle ranges from 10 nm to 150 nm.

8. The composition of claim 1 or 7, wherein a therapeutic agent is dispersed within the nanoparticle.

9. The composition of claim 8, wherein the therapeutic agent is covalently bound to the nanoparticle.

10. The composition of claim 8, wherein the therapeutic agent is not covalently bound to the nanoparticle.

11. The composition of claim 8, wherein the therapeutic agent comprises at least one selected from the group consisting of insulin, interferon, parathyroid hormone, calcitonin, serotonin, serotonin agonist, serotonin reuptake inhibitor, human growth hormone, GIP, anti-GIP monoclonal antibody, metformin, bromocriptine, dopamine, glucagon and GLP-1.

12. The composition of claim 8, wherein the nanoparticle is suspended in an aqueous solution comprising a free dissolved therapeutic agent that is not dispersed within the nanoparticle.

13. The composition of claim 8, wherein the therapeutic agent is insulin.

14. The composition of claim 12, wherein the therapeutic agent dispersed within the nanoparticle and the free dissolved therapeutic agent are independently selected from the group consisting of insulin lispro, insulin aspart, regular insulin, insulin glargine, insulin zinc, extended human insulin zinc suspension, isophane insulin, human buffered regular insulin, insulin glulisine, recombinant human regular insulin, recombinant human insulin isophane, and any combinations thereof.

15. The composition of claim 7, wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl).

16. The composition of claim 7, wherein the hepatocyte receptor binding molecule comprises biotin.

17. The composition of claim 16, wherein the biotin-containing hepatocyte receptor binding molecule comprises at least one selected from the group consisting of N-hydroxysuccinimide (NHS) biotin; sulfo-NHS-biotin; N-hydroxysuccinimide long chain biotin; sulfo-N-hydroxysuccinimide long chain biotin; D-biotin; biocytin; sulfo-N-hydroxysuccinimide-S-S-biotin; biotin-BMCC; biotin-HPDP; iodoacetyl-LC-biotin; biotin-hydrazide; biotin-LC-hydrazide; biocytin hydrazide; biotin cadaverine; carboxybiotin; photobiotin; *ρ*-aminobenzoyl biocytin trifluoroacetate; *ρ*-diazobenzoyl biocytin; biotin DHPE (2,3-diacetoxypropyl 2-(5-((3aS,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)ethyl phosphate); biotin-X-DHPE (2,3-diacetoxypropyl 2-(6-(5-((3aS,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)hexanamido) ethyl phosphate); 12-((biotinyl)amino)dodecanoic acid; 12-((biotinyl)amino)dodecanoic acid succinimidyl

ester; S-biotinyl homocysteine; biocytin-X; biocytin x-hydrazide; biotinethylenediamine; biotin-XL; biotin-X-ethylenediamine; biotin-XX hydrazide; biotin-XX-SE; biotin-XX, SSE; biotin-X-cadaverine; α-(t-BOC)biocytin; N-(biotinyl)-N'-(iodoacetyl) ethylenediamine; DNP-X-biocytin-X-SE; biotin-X-hydrazide; norbiotinamine hydrochloride; 3-(N-maleimidylpropionyl)biocytin; ARP; biotin-l-sulfoxide; biotin methyl ester; biotin-maleimide; biotin-poly(ethyleneglycol) amine; (+) biotin 4-amidobenzoic acid sodium salt; Biotin 2-N-acetylamino-2-deoxy-β-D-glucopyranoside; Biotin-α-D-N-acetylneuraminide; Biotin-α-L-fucoside; Biotin lacto-N-bioside; Biotin–Lewis-A trisaccharide; Biotin–Lewis-Y tetrasaccharide; Biotin-α-D-mannopyranoside; and biotin 6-O-phospho-α-D-mannopyranoside.

18. The composition of claim 16, wherein the biotin-containing hepatocyte receptor binding molecule comprises at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE.

19. The composition of claim 8, further comprising one of the following:

(a) cellulose acetate phthalate, which is at least partially bound to the therapeutic agent dispersed within the nanoparticle; and

(b) at least one charged organic molecule bound to the therapeutic agent dispersed within the nanoparticle, wherein the charged organic molecule is at least one selected from the group consisting of protamines, polylysine, poly (arg-pro-thr)$_n$ in a mole ratio of 1:1:1, poly (DL-Ala-poly-L-lys)$_n$ in a mole ratio of 6:1, histones, sugar polymers comprising a primary amino group, polynucleotides with primary amino groups, proteins comprising amino acid residues with carboxyl (COO^-) or sulfhydral (S^-) functional groups, and acidic polymers.

20. The composition of claim 13, wherein the insulin is selected from the group consisting of insulin lispro, insulin aspart, regular insulin, insulin glargine, insulin zinc, extended human insulin zinc suspension, isophane insulin, human buffered regular insulin, insulin glulisine, recombinant human regular insulin, recombinant human insulin isophane, and any combinations thereof.

21. The composition of claim 7, wherein the DSPC ranges from 40% to 75% (w/w) in the membrane.

22. The composition of claim 7, wherein the amount of the stearoyl lysophosphatidylcholine in the membrane is 5%-30% (w/w) of the amount of DSPC in the membrane.

23. The composition of claim 7, wherein the membrane comprises one of the following:

(a) cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, m-cresol, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE;

(b) cholesterol, dicetyl phosphate, DSPC, m-cresol, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE; and

(c) cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE.

24. A method of preparing the lipid-based nanoparticle of claim 7, the method comprising contacting cholesterol, dicetyl phosphate, amphipathic lipid, hepatocyte receptor binding molecule, and the at least one agent in an organic solvent-containing system; removing any organic solvent from the system to form a dried material; and suspending and homogenizing the dried material in an aqueous system.

25. The method of claim 24, wherein the at least one agent comprises a stabilizer, which is added to the organic solvent-containing system after the cholesterol, dicetyl phosphate, amphipathic lipid, stearoyl lysophosphatidylcholine if present, and hepatocyte receptor binding molecule had been contacted in the organic solvent-containing system.

26. The method of claim 4 or 24, wherein the nanoparticle comprises a therapeutic agent dispersed therewithin.

27. The method of claim 26, wherein one of the following applies:

(a) the therapeutic agent, cholesterol, dicetyl phosphate, amphipathic lipid, hepatocyte receptor binding molecule, and the at least one agent are simultaneously contacted in the organic solvent-containing system; and

(b) the nanoparticle is formed in the absence of the therapeutic agent, wherein the nanoparticle is at least partially concentrated, purified, or isolated, and wherein the therapeutic agent is contacted with the nanoparticle, whereby at least a portion of the therapeutic agent is dispersed within the nanoparticle.

28. The composition of any one of claims 2-3, 8-14 and 19-20, for use in therapy.

29. Use of a therapeutically effective amount of the composition of claim 13 in the manufacture of a medicament for the treatment of diabetes mellitus in a mammal, wherein the medicament is to be administered to the mammal in need thereof.