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) about 9.4 : 18.1 : 56.8 : 14.1 : 0.0 : 1.5;

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

(c) about 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 about 10 nm to about 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 cellulose acetate phthalate, which is at least partially bound to the therapeutic agent dispersed within the nanoparticle.

4. The composition of claim 1, wherein a therapeutic agent is dispersed within the nanoparticle, and further comprising 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.

5. A method of preparing the lipid-based nanoparticle of claim 1, the method comprising contacting in an aqueous system cholesterol, dicetyl phosphate, DSPC, biotin-DHPE, and the at least one agent.

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

7. The method of claim 5, wherein the nanoparticle comprises a therapeutic agent dispersed therewithin, and wherein the therapeutic agent, cholesterol, dicetyl phosphate, DSPC, at least one agent, and biotin-DHPE are simultaneously contacted in the aqueous system.

8. The method of claim 5, wherein the nanoparticle comprises a therapeutic agent dispersed therewithin, wherein 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.

9. 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 about 10% to about 25 % (w/w) in the membrane;

wherein, if present, the stearoyl lysophosphatidylcholine ranges from about 5% to about 30% (w/w) in the membrane;

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

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

10. The composition of claim 1 or 9, wherein a therapeutic agent is dispersed within the nanoparticle.

11. The composition of claim 10, wherein the therapeutic agent is covalently bound to the nanoparticle.

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

13. The composition of claim 10, 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.

14. The composition of claim 10, wherein the nanoparticle is suspended in an aqueous solution comprising a free dissolved therapeutic agent that is not dispersed within the nanoparticle.

15. The composition of claim 10, wherein the therapeutic agent is insulin.

16. The composition of claim 16, wherein the nanoparticle-dispersed insulin and the free dissolved insulin 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.

17. The composition of claim 9, 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).

18. The composition of claim 9, wherein the hepatocyte receptor binding molecule comprises biotin.

19. The composition of claim 18, 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.

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

21. The composition of claim 9, further comprising cellulose acetate phthalate, which is at least partially bound to the therapeutic agent dispersed within the nanoparticle.

22. The composition of claim 10, further comprising 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.

23. The composition of claim 9, wherein the cholesterol ranges from about 5% to about 15% (w/w) in the membrane.

24. The composition of claim 9, wherein the dicetyl phosphate ranges from about 10% to about 25% (w/w) in the membrane.

25. The composition of claim 9, wherein the DSPC ranges from about 40% to about 75% (w/w) in the membrane.

26. The composition of claim 9, wherein the hepatocyte receptor binding molecule ranges from about 0.5% to about 4% (w/w) in the membrane.

27. The composition of claim 9, wherein the amount of the stearoyl lysophosphatidylcholine in the membrane is about 5%-30% (w/w) of the amount of DSPC in the membrane.

28. The composition of claim 9, 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.

29. A method of preparing the lipid-based nanoparticle of claim 9, the method comprising contacting in an aqueous system cholesterol, dicetyl phosphate, amphipathic lipid, hepatocyte receptor binding molecule, and the at least one agent.

30. The method of claim 29, wherein the at least one agent comprises a stabilizer, which is added to the aqueous system after the cholesterol, dicetyl phosphate, amphipathic lipid, stearoyl lysophosphatidylcholine if present, and hepatocyte receptor binding molecule had been contacted in the aqueous system.

31. The method of claim 5 or 29, wherein the nanoparticle comprises a therapeutic agent dispersed therewithin.

32. The method of claim 31, wherein the therapeutic agent, cholesterol, dicetyl phosphate, amphipathic lipid, hepatocyte receptor binding molecule, and the at least one agent are simultaneously contacted in the aqueous system.

33. The method of claim 31, wherein 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.

34. The composition of any one of claims 1-4 and 9-28, for use in therapy.

35. Use of a therapeutically effective amount of the composition of claim 10 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.

36. The use of claim 35, wherein the therapeutic agent comprises insulin.

37. Use of a therapeutically effective amount of the composition of claim 10 in the manufacture of a medicament for the treatment of diabetes mellitus in a mammal, wherein the medicament activates hepatic glycogen synthase in the mammal, the medicament is to be administered to the mammal in need thereof, and wherein the therapeutic agent comprises insulin.